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Volume - 2

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Chapter - 1
A Literary Review on *Shodhana* of *Bhallataka*
(*Semicarpus anacardium*) and *Kupilu* (*Strychnous*
***nuxvomica*)**

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Chapter - 1

A Literary Review on *Shodhana* of *Bhallataka* (*Semicarpus anacardium*) and *Kupilu* (*Strychnous nuxvomica*)

Dr. Sneha Vidhate, Gauri Lokhande and Dr. Priyanka Wate

Abstract

Bhallatak (*Semicarpus anacardium*) and Kupilu (*Strychnous nuxvomica*) is reported under upavish dravya (Semipoisonous drugs) in Ayurvedic classical literature and pharmacopeia. It is advocated that *shodhan* (purification method) of *bhallatk* fruits and *kupilu* seeds done in various media as per ayurvedic literature. The impact of *shodhana* was appraised by pharmaceutical, physico-chemical and chromatographical parameters and the chemical changes during *shodhana*. Increased level of anacardol was observed in *Shodhita* (processed) fruits in comparison to the raw fruits. So, there is need to evaluate a various methods of *shodhan* (purification). *Vatsanabh* (*Aconitum* species), *Semicarpus anacardium*, *strychnous nuxvomika*, *Acorus calamus*, *Abrus precatorius* etc. are some of the very interesting examples of toxic plants which are used in various Indian system of medicine for treating purpose. But if they are used without *shodhan* (Purifications) the toxicity and various complication can occur. So *shodhan* has a prime importance in Ayurveda. *Shodhana* merely not only remove toxicity from drugs but also enhance the quality of drugs.

Keywords: Chromatographical, pharmacopeia, shodhana

Introduction

Screening the literature, it was observed that the concept of *Shodhana* is mentioned for the first time in the Charaka Samhita ^[1]. It is mentioned in aragvadhya adhyaya as a content of one of the lepa in sutra sthana ^[2]. It is very interesting to observe that the specific media are used for *shodhan* (Processing and purification) of particular poisonous drugs, like gomutra for *shodhan* of *Vatsanabh* (*Aconitum ferox* wall) and godugdha for *Kupilu* (*Strychnos nuxvomika* Linn) ^[3]. The most commonly used liquid media for *shodhana* are cow urine and cow milk. Latest research has proved that gomutra possesses bio-enhancer properties along with antibacterial and antifungal effects ^[4].

Definition

It is a process in which Kshalana (Washing), Mardana (Pounding), Bhavana (Levigation), Swedana (Boiling), Bharjana (Frying), Nirvapa (Heating & Dipping in specified liquids), etc. are carried out on mineral drugs with a view to eliminating impurities.

Motilal Banarasi Das Publication, Varanasi, Sharma Sadananda, Rasa Tarangini.

Poisonous drugs must be understood because, when used correctly and at the prescribed dose, they can be powerful therapeutic agents. It is a fact that virtually any substance can be harmful at high enough concentrations; as rightly quoted, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy" [6].

We can find explanations for the use, importance, and therapeutic consideration of visha dravyas (poisonous substances) in much of the classical literature. In Ayurvedic Science-origin, properties, purification, uses, toxic symptoms, etc., detailed descriptions are available, especially in Rasashastra, the use of Visha-Upavisha dravyas (poisonous & semi-poisonous substances) in the Rasa karma as well as Rasa bhandhan has got prime importance. They included and classified visha dravyas on the basis of their usefulness in Rasa karma [7].

Visha-Upavisha dravyas, from a therapeutic point of view, are considered highly valuable in accordance with their quick effectiveness even in smaller doses. But at the same time, they are very dangerous as they may prove fatal to human beings if used without proper care and in higher doses. Therefore, understanding the visha dravyas, its important uses, medicinal applications, benefits, and toxic symptoms is crucial [8].

Bhallataka and kupilu are widely used as herbal medicinal drugs in Ayurveda, but both are too toxic if used without proper shodhana (Purification), then it is harmful to the patients. Various methods for purifying both drugs were mentioned in Bhrutaryi, Nighantus, and the Modern Textbook. Bhallataka (*Semecarpus anacardium* Linn.) is one of the wonderful drugs used to cure many diseases like inflammation, piles, cancer etc. in the Indian system of medicine. Before administering the drug to the patients, shodhana (purificatory procedures) is a must. The oily fraction in the pericarp of the fruit is responsible for the toxic nature of the drug. In southern parts of India, to purify Bhallataka fruit, the frying method is traditionally followed. Nux vomica was introduced in Europe in the sixteenth century but was not used much in medicine, being chiefly

employed to poison dogs, cats, crows, and other small animals ^[9]. It is cited in the treatises of Ayurveda that the 'Visha' (poison) becomes 'Amrita' (nectar) after logical administration ^[10], and the ancient physicians of Ayurveda successfully used this drug in a number of diseases after proper purification in some specific media. Either *S. nux-vomica* or its alkaloids have been reported for their analgesic and anti-inflammatory properties. It is possible that a greater percentage of oil might be reduced by soaking the fruits in the Gomtra or Godugdha. Brick powder has an adsorbent property because of which it absorbs irritant oils in the fruit. Odhana has no effect on total flavonoids or total carbohydrate content; however, a significant decrease in total phenolic content has been reported following the odhana process.

Involving different media specific to substances such as Godugdha (milk of *Bos indicus*), Gomtra (urine of *Bos indicus*), Triphal (combination of three fruits; *Terminalia chebula*, *Terminalia bellarica*, and *Embolia officinalis*) and lemon juice, etc. ^[11, 12], [Table 3]. A number of toxicological and pharmacological studies have been conducted on the active phytochemicals of many poisonous plants after their odhana. The objective of the present study is to review the state of knowledge about the odhana process of many poisonous plants. The present review also describes up-to-date information regarding the different processes of detoxification (odhana) in the Ayurvedic system of medicine.

Review of literature

The history of visha & its treatment goes back centuries.

The mythological concept regarding the origin of Visha states that it was created at the time of the creation of the universe by Lord Brahma ^[13] and some opinion that it was obtained during Samudra Manthana. The Vedas also contain references to visha, or poison, and poisoning ^[14].

Ayurveda dedicates one of its branches to Danshtra Agadtantra or vishatantra, Viṣagara vairodhika prashamana, which is dedicated solely to the concept and treatment of visha.

These references provided ample evidence to prove that toxicology was a well-developed branch in ancient India ^[15].

Aim: To study a literary review on shodhan (Purification) of Bhallataka (*Semicarpus anacardium*) and Kupilu (*Strychnous nuxvomica*).

Objective

To study the shodhan (Purification) of Bhallataka (*Semicarpus anacardium*) and Kupilu (*Strychnous nuxvomica*).

To study the effects of different methods used for shodhan of Bhallataka (*Semicarpus anacardium*) and Kupilu (*Strychnous nuxvomica*).

Material & methodology

The poisonous plants reported in ancient scriptures of Ayurveda are still being used widely in a number of diseases after processing with proper Shodhana. Ayurvedic physicians successfully employed these drugs after proper Shodhana. General processing of poisonous substances before consumption.

On Review of Ayurvedic literature it is observed that various Shodhana procedures are mentioned for visha and Upavisha group of drugs. Out of these, following procedures are common for different 'Vishopavisha' drugs.

Gomutra Nimajjana: soaking in cow urine for a prescribed period.

- **Swedana:** Boiling in different liquids such as cow milk, goat milk, cow urine, vegetable extracts and Kanjika etc.
- **Bharjana:** Frying with or without ghee.
- **Bhavana:** Maceration and/or trituration with vegetable juices.
- **Nihnsnehana:** Reduction of oily content.
- **Kshalana:** Washing with hot water.
- **Nistvachikarana:** Is the process of decortications (removal of covering).

Out of the procedures described above, cow urine and boiling with cow milk are the most common procedures applied for almost all the 'Vishopavisha' drugs ^[17].

Various media used for shodhan

Gomutra (cow's urine), Gokshira (cow's milk), Nariela udaka (coconut water), Goghrita (cow's ghee), Choornodaka (lime water), Adraka swarasa (Ginger juice), Ishitika choorna (brick powder), Triphala kwatha (Triphala decoction), Panchapallava kwatha, Ushna jala (hot water) Aja kshira (goat's milk), Kanji (sour gruel), Errands tailam (castor oil) ^[18].

Shodhan of Bhallatak & Kupilu through different methods

Shodhana is a unique concept mentioned in classical texts of Ayurveda where poisonous/semi poisonous drugs are passed through some specific recommended purificatory procedures to reduce or nullify the possible toxic effects. To minimize the possible adverse reactions of Bhallataka & Kupilu different purificatory methods are advised before its internal administration. there are some methods mentioned as follow:

Methods explain by rasa tantra saara evam siddha prayoga sangraha

- 1. First shodhana method:** In this method, ripened fruits of bhallataka are taken. They are subjected to put in the water. It is for the differentiation of grahya and agrahya bhallataka as per the classics. The sunken fruits of bhallataka are taken for shodhana process. They are dried well in shade and then thoroughly rubbed with brick powder. By this method bhallataka fruits get purified. Special mention is given here that shodhita bhallataka by this method are to be used for preparing kwatha (decoction) and further used in paaka etc. ^[19].
- 2. Second shodhana method:** In this method, fruits of bhallataka are put into a pottali made-up of cloth and subjected to heat in the dola yantra with media as buffalo-dung dissolved in four times water. It is to be heated on mild heat for twelve hours. Then bhallataka fruits are removed from it and subjected for further process of mild heating in dola yantra with different media as gaumutra (cow-urine) and gaudugdha (cow-milk); each for four prahara (twelve hours). Then they are washed carefully with hot water and thalamus is removed carefully. Then these fruits are subjected to heat in the dola yantra with media as coconut water. By this way the fruits of bhallataka get purified. Special mention is given here that shodhita bhallataka by this method are to be used for mixing in churna (powder) formulations ^[20].

Method III: Pottali is prepared by placing Bhallataka fruits and Ishtika churna (Brick powder) in a clean cloth. This Pottali is rubbed by hand by applying moderate pressure. When brick powder become wet with oil and the skin of Bhallataka fruit is peeled off, it is washed with hot water and stored

Method IV: Bhallataka fruits are cut in two pieces, placed in Dolayantra and sedated on mild fire with coconut water ^[21].

Method V: After removing the attachment of thalamus, Bhallataka fruits are soaked in Gomutra (Cow's urine) for 7 days and thereafter in Goudugdha (Cow's Milk) for 7 days. The seeds then put into bag containing coarse brick powder with which they are rubbed carefully, with a view to reduce the oil content, then the fruits are washed with water and dried in air ^[22].

Method VI: Traditional purificatory method i.e. frying the Bhallataka fruit is followed traditionally in southern parts of India ^[23].

Kupilu Shodhana (Detoxification/Purification method)

Method I: Fry Kuchala seeds with ghee in a pan on slow flame till it's outer covering become led-yellow coloured. Take these seeds and remove the outer skin of seeds and grind the hot pulp immediately. This shodhana process is useful in emergency use of Kuchala.

Method II: Wrap Kuchala seeds in a cloth, keep it in Dolayantra with cow's milk, and boil it for 3 hrs. After 3 hrs remove the seeds, grind it in iron Kharal, and use the churna (powder). Skin of seeds is removed. It is boiled with milk for 7 days, dried, then it is fried in ghee and powdered.

Method III: Keep kuchala seeds in mutra for seven days then boil it in godugdha and after that fry it in ghrith according to bhavprakash ^[24].

Study design: Review Study.

Data collection: Data will be collected from ayurvedic literature, internet and various text books, journals and data base.

Discussion

Whole review reveals that the Vishas and Upavishas are very useful as a part of use in the herbo-mineral preparations though needs to detoxified and purified. The Ayurved classical purification and detoxification classical method makes it suitable to use on human body for the treatment of various ailments & discussion will be done on the basis of review study. It can be seen clearly that by purifying bhallataka with the first method, which is earlier described in the Rasa Tarangini book, only a limited quantity of purifications may happen because of very simple process and use of only one shodhan media. so whichever the toxic elements found in the seed of bhallatak is removed through different procedure with different materials. But here it is specifically mentioned that this type of shodhita bhallataka is used only for kwatha type formulations. Even as purifying bhallataka with the second method, intense purification is done by boiling the bhallataka on mild heat in dola yantra for 48 hours. This type of intense purification is certainly needed while mixing in churna are generally to be consumed directly without any pharmaceutical process. In Kuchala shodhan also the moisture content in Kupeelu was increased after purification with Kanji, but decreased when the seeds were processed in Ardraka swarasa. Therefore, better extraction of alkaloids, along with other chemical constituents, took place when the raw samples were kept in Kanji. However, reduction in the alkaloid content like strychnine and brucine was only observed when the samples were processed in Ardraka swarasa. Therefore, a hypothesis can be

drawn that as far as reduction in concentrations of toxic alkaloids are concerned either by extraction or by transformation into another form *Ardra* *swarasa* may be a better media than *Kanji*.

Shodhana is a preliminary step towards therapeutic administration. *Shodhana* is a process in which Physical & Chemical impurities & toxins will be removed. Historically the detailed description of *shodhana* can be traced in *Rasashastra* texts and got developed immensely during medieval period i.e. 8th century onwards.

Conclusion

In present study it is concluded that the *shodhan* of both *bhallatak* and *kupilu* was scripted in different text according to various acharyas. There are various method of *shodhan* (Purification) of poisonous drugs such as dipping into *gomutra*, *eith dola yantra*, *bhurjan* method. *Ghee* are the media in which the various poisonous and non-poisonous drugs were purified due to its *yogvahi* property. Both drugs itself has a immense uses as a medicinally so its purification required by different processed. There are need to evaluate a study in future that which was the best and complete purificatoiry methods of poisonous drugs. It may be concluded that the traditional system of purification (*Śodhana*) can influence the phytochemical, pharmacological, and toxicological profile of the plant drugs and thereby useful in increasing safety profile and efficacy of the drugs. It is worthwhile to adopt *Śodhana* processes as per Indian system of medicine in the development of herbal formulations with application of modern technology to assess its safety and efficacy. Studies have shown that the toxic constituents are transferred into media rendering the drug nontoxic. Specific media has definitely an important role in making a drug act without causing side-effects/adverse effects.

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Chapter - 2

Role of *Cassia* Species in Drug Discovery

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Chapter - 2

Role of *Cassia* Species in Drug Discovery

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Abstract

The document explores the diverse pharmacological potential of the *Cassia* genus, highlighting its significant role in traditional and modern medicine. *Cassia* species, extensively utilized in systems such as Ayurveda, Unani, and Traditional Chinese Medicine, exhibit therapeutic properties for gastrointestinal, respiratory, and skin disorders. The phytochemical richness of *Cassia* includes terpenoids, glycosides, flavonoids, and anthraquinones, which contribute to its antimicrobial, anti-inflammatory, antioxidant, antidiabetic, and hepatoprotective activities. With over 160 bioactive compounds identified, the review underscores the need for further research into unexplored species, bioactive components, and potential health applications.

The paper also emphasizes the increasing global demand for herbal remedies due to their safety and effectiveness compared to synthetic drugs. The applications of *Cassia* species span across medicine, nutraceuticals, and industrial uses. It concludes that *Cassia* holds untapped potential for future drug discovery, urging advanced pharmacological studies to harness its full therapeutic spectrum.

Keywords: *Cassia* species, phytochemical properties, traditional medicine, pharmacological activities, herbal drug discovery

Introduction

Indian traditional medicine is based on various systems including Ayurveda, Siddha, Unani and Homoeopathy. The evaluation of these drugs is primarily based on phytochemical, pharmacological and allied approaches including various instrumental techniques such as chromatography, microscopy and others. With the emerging worldwide interest in adopting and studying traditional systems and exploiting their potential based on different health care systems, the evaluation of the rich heritage of traditional medicine is essential (Bajracharya and Gupta, 2021). In this regard, one such plant is *Cassia fistula*.

Cassia is a tropical aromatic evergreen tree of the Caesalpinaceae family, commonly used in traditional Chinese medicine. It is also a traditional spice, widely used around the world. The modern research on *Cassia*, including the traditional uses, phytochemistry, pharmacology and toxicology. In addition, some significant issues and the potential direction of future *C. cassia* research. More than 160 chemicals have been separated and identified from *Cassia*.

The main constituents of *Cassia* are terpenoids, phenylpropanoids, glycosides, etc. Modern studies have confirmed that *Cassia* has a wide range of pharmacological effects, including antitumour, anti-inflammatory and analgesic, anti-diabetic and antiobesity, antibacterial and antiviral, cardiovascular protective, cytoprotective, neuroprotective, immune regulatory effects, anti-tyrosinase activity and other effects. However, the modern studies of *Cassia* are still not complete and more in-depth investigations need to be conducted in alimentotherapy, health product, toxicity and side effects, and more bioactive components and potential pharmacological effects need to be explored in the future (Zhang *et al.*, 2019).

Archer *et al.*, (2019) studied that the *Cassia*, mostly found in Africa has been used in traditional medicine as purgative, diuretic, analgesic, antibiotic, anti-inflammatory agent and many others for decade. It is used as a traditional therapeutic benefits, Ethnopharmacological studies, pharmacological, toxicological and phytochemical relevance. Various studies on *Cassia* gave a detailed understanding of its constituents which serves as evidence for its therapeutic and safety importance as well as a source of novel compounds with therapeutic effects. *Cassia* is significant not only in providing a comprehensive data for continuous research but also will show untapped areas in the research on *Cassia*.

Zibae *et al.*, (2023) reported that *Cassia* species have a long history of utilization in various traditional medicine systems worldwide, and they are widely consumed for medicinal purposes, particularly the officinal species. This is to provide a comprehensive overview of the botany, traditional uses, photochemistry, and pharmacology of the *Cassia* genus. It is important that the taxonomy of the *Cassia* genus has undergone changes over time, resulting in the reclassification of some plants into the *Senna* and *Chamaecrista* genera.

The findings that *Cassia*, *Senna*, and *Chamaecrista* spp. have been extensively used for medicinal purposes in various traditional medicine systems, including Traditional Chinese Medicine (TCM), Islamic Traditional Medicine (ITM), Unani medicine, and Ayurveda. These plants have traditionally been employed to treat respiratory and gastrointestinal

conditions, as well as skin disorders. In ITM, the reported species include *Cassia acutifolia*, *Cassia fistula*, *Senna occidentalis*, and *Senna tora*. In TCM, the most commonly used species are *Cassia occidentalis*, *Cassia tora*, *Senna alexandrina*, *Senna occidentalis*, *Senna auriculata* and *Senna singueana*. These plants are rich in phytochemicals such as anthraquinones, alkaloids, and flavonoids, which contribute to their diverse pharmacological activities.

These activities include antimicrobial, anti-inflammatory, antioxidant, antidiabetic, antiulcer, hypolipidemic, anti-atherosclerotic, and hepatoprotective effects. Based on the available literature, it can be concluded that the *Cassia* genus possesses significant preventive and therapeutic potential. The rich phytochemical composition and wide range of pharmacological activities make *Cassia* species a valuable resource in the field of natural medicine.

Due to the numerous unfavorable impact of present day drugs individuals used to incline toward herbal medications. The traditional prescriptions are progressively requested through the traditional experts and herbalists in the treatment of irresistible ailments. Medicinal plants assume a fundamental part for the improvement of new medications. *Cassia* is a medicinal plant and belongs to a Caesalpiniaceae family, generally employed as a part of medicine ayurvedic system on behalf of different infirmities. Siddiqua *et al.*, (2018) reported that *Cassia* is a medium size short-lived tree with long and cylindrical fruits containing pulp and furthermore with a splendid yellow shaded flower. The tree is local to Pakistan, generally discovered east of the Indus in the fields and proceeding with north into the Himalayas to a rise of roughly 1200 meters. In Pakistan it is developed all through the field region.

The present article gives a record of refreshed data on its phytochemical and pharmacological properties. The audit uncovers that wide quantities of phytochemical constituents have been separated from the plant perform activity such as destroying parasitic worms especially of the intestine, reduce fever, inhibit oxidation, killing larval pests, destroying fungi, anti-leishmanian function, destroying bacteria and other microbes, also anti-fieri activity, activity against tumor, as well as cough suppressant, activity of central nervous system, impact of clastogenic, having tendency to loosen or relax means producing bowel.

Danish *et al.*, (2011) studied that medicinal herbs are moving from fringe to main stream use with a greater number of people seeking remedies and health approaches free from side effects caused by synthetic chemicals. India officially recognizes over 3000 plants for their medicinal value. It generally

estimated that over 6000 plants in India are in use in traditional, folk and herbal medicine.

The phytochemical and pharmacological aspects of *Cassia*. It is obtained from deciduous and mixed-monsoon forests throughout greater parts of India, ascending to 1300 m in outer Himalaya, is widely used in traditional medicinal system of India has been reported to possess hepatoprotective, anti-inflammatory, antitussive, antifungal and also used to check wounds healing and antibacterial. It is known as a rich source of tannins, flavonoids and glycosides. The innumerable medicinal properties and therapeutic uses of *Cassia* as well as its phytochemical investigations prove its importance as a valuable medicinal plant.

Distribution of *Cassia*

Lodha *et al.*, (2010) reported that *Cassia* is a large genus of around 500 species of flowering plants in the family Leguminosae and is widely distributed throughout Asia including India, Mauritius, China, East Africa, South Africa, America, Mexico, West Indies and Brazil. *Cassia* species belong to the family Caesalpiniaceae. Caesalpiniaceae is often treated as a sub-family, Caesalpinoideae, of the large family Leguminosae. It is closely related to Mimosaceae and Papilionaceae, but can be distinguished by few stamens and five free petals. Caesalpinoideae consist of trees, shrubs and a few woody herbs found in the tropics. Economically, woody Caesalpiniaceae is important for its timber. *Cassia* and *Tamarindus* species are used for medicinal purposes.

Medicinal values of *Cassia* varieties

Demands of traditional herbal medicines are increasing day by day not only by the developing countries but also by the developed countries throughout the world. The demand is due to the increased acceptance of ayurveda and traditional herbal medicines, because of having their safe therapeutic effect and no side effects, as such modern peoples relies more on drug resources of plant origin (Jang *et al.*, 2007). The World Health Organization (WHO) estimates that about 80% of people living in developing countries rely exclusively on traditional medicines for their primary health care need (Pawar and D'mello, 2011).

Medicinal plants are the richest bio-resource of drugs of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs. Medicinal plants have provided the modern medicine with numerous plant-derived therapeutic agents (Oladunmoye *et al.*, 2009). Natural

products play a dominant role in the development of novel drug leads for the treatment and prevention of diseases (Gilani, 2005). Interestingly it is estimated that more than 25% of the modern medicines are directly or indirectly derived from plants. It is worth mentioning that Indian medicinal plants are considered as a vast source of several pharmacologically principles and compounds that are commonly used as home remedies against multiple ailments.

India is virtually a herbarium of the world, using plants and herbs as the basic source of medicine. Herbals which form a part of our nutrition and provide us an additional therapeutic effect are in demand and *Cassia* species is one of such plant (Harshal *et al.*, 2011). *Cassia* species have been of keen medicinal interest in phytochemical and pharmacological research due to their excellent medicinal values. Plants belonging to *Cassia* species are used extensively in various parts of the world against a wide range of ailments, the synergistic action of its metabolite being probably responsible for the plants beneficial effects.

They are well known in folk medicine for their laxative and purgative uses (Verma *et al.*, 2010). *Cassia* species (Caesalpinaceae) are commonly found in India and other tropical countries (Nadkarni, 1954). Various medicinal properties have been attributed to this plant in the traditional system of Indian medicine. Several anthraquinones have been isolated from the seeds of *Cassia* species. Sennosides, which are well known for their medicinal importance, have been detected in the leaves of the plant (Raghunathan *et al.*, 1974). *Cassia* species are already reported in the ancient ayurvedic literatures and literature survey indicated its use against various skin diseases such as ringworm, eczema, and scabies. Because of the high incidence of skin diseases, especially among the weaker section of the Indian population, it was felt worthwhile undertaking research on this plant.

According to ayurveda the leaves and seeds are acrid, laxative, antiperiodic, anthelmintic, ophthalmic, liver tonic, cardiogenic and expectorant. The leaves and seeds are useful in leprosy, ringworm, flatulence, colic, dyspepsia, constipation, cough, bronchitis, cardiac disorders. *Cassia* species powder made from *Cassia* species seeds and *Cassia* species splits are some ancient natural ingredients. In India, *Cassia* species is used as a natural pesticide in organic farms. Roasted seeds are substituted for coffee, like tephrosia seeds. *Cassia* species powders are most popularly used in the pet-food industry. It is mix with guar gum for use in mining and other industrial application.

The extracts of *Cassia* species have been used as a remedy for various skin ailments, rheumatic disease and as laxatives (Maity *et al.*, 1997). *Cassia* plants possess unlimited and untapped wealth of chemical compounds with high drug potential which make these plants useful as sources of biomedicines. *Cassia* species have been of keen interest in phytochemistry due to their excellent medicinal values. All *Cassia* species are an important rich source of secondary metabolites, notably anthraquinone derivatives and has been used in Chinese and Ayurvedic preparations. Phytochemistry of some medicinally important *Cassia* species has been presented, considering the fact that there are about 580 species of this genus scattered all around the world. Only 46 species have been phytochemically studied. Hence, an attempt has been made to overview phytochemical studies in *Cassia* species which serves as a potential source for contribution in the modern system of herbal medicine (Deshpande and Bhalsing, 2013).

Medicinal plant species contain vast and unexploited riches of chemical substances with high medical potential making these plant species valuable as biomedicine sources. *Cassia* is an important medicinal plant used in many traditional medicinal systems including Ayurveda and Chinese Traditional Medicine. It is a deciduous medium sized tree with elongated and rod-shaped fruits having pulp and have bright yellow flowers, earning the name “Yellow Shower”. It provides information on its botanical description and pharmacological properties including antioxidant, antimicrobial, anti-inflammatory, antidiabetic, antitumor, hepatoprotective among other activities. Pharmacology on medicinal plants will provide valuable information; thus, *Cassia* can provide important discoveries of valuable bioactive natural products facilitating in developing novel pharmaceuticals products (Mondal, 2014).

Medicinal plant species contain a variety of chemical substances with high medical potential, making these plant species valuable as biomedical sources. This plant is a deciduous plant also known as “Yellow Shower”. The plant *Cassia* is considered for its biological importance in the traditional medication system. This plant is full of different bioactive phytochemicals. In Ayurveda, the plant has also attained medicinal importance. Pharmacological properties like antioxidant, antimicrobial, anti-inflammatory, antidiabetic, antitumor, hepatoprotective, and many more are exhibited by the plant *Cassia* (Singh *et al.*, 2023). *Cassia* is a plant in the family fabaceae. It is commonly known as the Golden Shower, Indiana Laburnum, Rajavriksha. It is native to India, the Amazon and Sri Lanka and diffused in various countries including Mexico, China, Mauritius, East Africa, South Africa and West Indies. *Cassia* plants are used as ornamental and shade tree around the houses and also used

in the event “Vishukkani” on the day of vishu (First day of zodiac calendar), which literally means that "the first thing seen on the day of Vishu after waking up". Medicinally it has been various pharmacological activities like antifungal, antioxidants, antimicrobial, anti-inflammatory, anti tumour, hepatoprotective, hypoglycemic activity. It is recommended for the treatment of Jaundice, Gout, Fatty Liver, Liver Disorder, Bronchitis, Skin disease and so on. In Ayurvedic medicine, Golden Shower Tree is known as "disease killer" and it pacifies the 3 doshas of vaat, pitta and kapha.

It expels the pitta and kapha from the body. Its fruit pulp is used as mild laxative as well as cardiac conditions and stomach problems such as acid reflux. Flowers used for fever, root as a diuretic. The bark and leaves are used for skin diseases. The seeds are recognised as antibilious, aperitif, carminative, and laxative while the root is used for curing adenopathy, burning sensations, leprosy, skin diseases, syphilis, and tubercular glands. The leaves of the tree is used for erysipelas, malaria, rheumatism, and ulcers, the buds are used for biliousness, constipation, fever, leprosy, and skin disease and the fruit for abdominal pain, constipation, fever, heart disease, and leprosy. Thus every part of this plant is recognized for its medicinal properties.

Plant has rich source of tannins, flavanoids and glycosides present in *Cassia fistula* might be medicinally important and/or nutritionally valuable. The plant is rich in carbohydrates, Linoleic, Oleic, and Stearic. Flower pollen contains phenylalanine, methionine, glutamic acid and proline. Leaf of *Cassia fistula* mainly contains Oxalic Acids, Tannins, Oxyanthraquinones, Anthraquinones Derivatives. Fruit of *Cassia fistula* contains Rhein Glycosides, Fistulic Acids, Sennosides A B, Anthraquinones, Flavanoid-3-ol-derivatives. Ceryl Alcohol, Kaempferol, Bianthraquinone Glycosides, Fistulin, Essential Oils, Volatile Components, Phytol (16.1%), 2-Hexadecanone (12%), Crystals, 4-Hydroxy Benzoic Acids Hydrate have been reported from the plant. The main aim of this article is to highlight the latest review of scientifically proved medicinal activity against various diseases (Moshahid *et al.*, 2009).

Cassia is used as tonic, carminative and stimulant. Its leaves, seeds, and roots are used medicinally, primarily in Asia. It is believed to possess a laxative effect, as well as to be beneficial for the eyes. As a folk remedy, the seeds are often roasted, then boiled in water to produce a tea. Roasted seeds have also been used as a substitute for coffee. According to ayurveda the leaves and seeds are acrid, laxative, antiperiodic, anthelmintic, ophthalmic, liver tonic, cardio-tonic, expectorant, leprosy, ringworm, flatulence, colic, dyspepsia, constipation, cough, bronchitis (Shibata *et al.*, 1969). According to Chinese material medica, it promotes blood circulation, and its cold nature

makes it effective in the treatment of heat syndromes. Seed tarts ailments due heat such as blindness, conjunctivitis, hyperdacryosis (Nadkarni, 1954).

Cassia species have been of keen medicinal interest in phytochemical and pharmacological research due to their excellent medicinal values. Plants belonging to *Cassia* species are used extensively in various parts of the world against a wide range of ailments, the synergistic action of its metabolite being probably responsible for the plants beneficial effects. They are well known in folk medicine for their laxative and purgative uses (Verma *et al.*, 2010). Besides, they have been found to exhibit anti-inflammatory (Somachit and Sahid, 2003), antioxidant (Yen and Chuang, 2000), hypoglycemic (Jalalpure *et al.*, 2004), hyperglycemic (Somachit and Sahid, 2003), antiplasmodial (Iwalewa *et al.*, 1997), larvicidal (Yang *et al.*, 2003), antimutagenic (Silva *et al.*, 2008) and anticancer activities (Prasanna *et al.*, 2009). They are also widely used for the treatment of wounds (Joshi 2000), skin diseases such as ringworm, scabies and eczema, gastro-intestinal disorders like ulcers, uterus disorders (Elujoba *et al.*, 1999) rheumatism, anorexia and jaundice (Pieme *et al.*, 2006).

Pharmacological activities

The central analgesic action of the seeds of *Cassia sophera* studied by Eddy's and Leimbach using hot plate and method of Davis using Analgesimeter showed strong analgesic effect most probably of opioid type as the positive effect against the thermal nociceptive stimuli are indicative of opioid type of analgesic effect (Chopra, 1956).

Pai *et al.*, (2016) reported that compound shows good antimicrobial activity against gram -ve and gram +ve bacteria as compared with standard Gentamicin. The zones of inhibition of poly herbal formulations were in between 23-28 mm which can be comparable with standard formulation 24-29 mm. The antibacterial activity could be due to different classes of compounds present in leaves extracts, such as alkaloids, flavonoids, phenols and tannins. The use of semisolid formulations can increase the residence time of drugs on the skin and consequently enhance bioavailability. Poly-herbal ointments prepared by incorporating ethanolic extracts of leaves were effective can be used as antibacterial agent for the treatment of wounds and burns.

Cassia sophera has both peripheral and central analgesic properties. Its peripheral analgesic activity was deduced from its inhibitory effects on chemical-induced nociceptive stimuli. The acetic acid-induced abdominal contractions elucidate peripheral activity while the formalin test investigates

both. Acetic acid causes increase in prostaglandins such as PGE₂ and PGF₂, serotonin, and histamine in the peritoneal fluid, which brings about characteristic writhing in mice.

Drugs that primarily act on the central nervous system inhibit both phases equally while peripherally acting drugs inhibit last phase. The formalin test is a very useful method for not only assessing antinociceptive drugs but also helping in the elucidation of the action mechanism. The neurogenic phase is probably a direct result of stimulation in the paw and reflects centrally mediated pain with the release of substance P while the late phase is due to the release of histamine, serotonin, bradykinin and prostaglandins.

Ethanol extract of leaves of *Cassia sophora* blocks both the phases of formalin response but effect was more prominent in second phase (Nandakarni, 1954). The Methanolic extract of the leaves of *C. tora* showed good activity against carageenin, serotonin, histamine and dextran induced rat hind paw oedema in a dose dependent manner (Jain and Patil, 2010). The ethanol extract of leaves of *Cassia sophora* could effectively control the AST, ALT, ALP, and total bilirubin levels and increase the protein levels in the protective studies. The histo-pathological studies substantiated the activity of the drug. This scientifically supports the usage of this plant in traditional medicine for the treatment of liver disorders and as a tonic. Diamond and Rajan (2009) observed that (in vivo model of rat) *C. tora* leaves methanol extract was effective in protecting liver against Carbon tetrachloride (CCl₄) induced liver damage. Further, Dhanasekaran *et al.*, (2009) have carried out in-vivo study (hepatotoxicity induced by carbon tetrachloride in rats) and observed that Ononitol monohydrate (a class of glycoside isolated from *C. tora* leaves) decreases the levels of serum transaminase, lipid peroxidation and Tumor Necrosis Factor- α (TNF- α) while it increases the levels of antioxidant and hepatic glutathione enzyme activities.

Histo-pathological findings put forward the hepatoprotective activity of ononitol monohydrate with- out any adverse effect (Dhanasekaran *et al.*, 2009). Malhotra and Misra, (1982) reported that the antidiabetic principles present in ethanol extract (90%) of the leaves of *Cassia sophora* exhibits significant hypoglycemic activity by increasing peripheral glucose. The antidiabetic activity may be due to β -cell restoration of pancreas against streptozocin induce damage (Joshi *et al.*, 1985). It also has an antilipidemic activity. The investigation validates the use of *Cassia sophora* as a herbal drug for antidiabetic and antilipidemic activity

Herbal formulation on *Cassia*

Sahana *et al.*, 2014 investigated a simple formulation of bactericidal cold cream using the biosynthesized silver nanoparticles (AgNPs) from *Cassia auriculata* flower extract and their antibacterial activity was tested against various clinical pathogens such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis*. An eco-friendly method was followed for the biosynthesis of AgNPs using *C. auriculata* flower extract as a reducing agent at room temperature. The effect of different concentrations of flower extract and the various pH conditions of the reaction medium toward the formation of NPs were studied. Surface plasmon resonance peaks were obtained from 403 nm to 428 nm. Further, the synthesized NPs were characterized by dynamic light scattering particle size analysis, Zeta potential analysis, atomic force microscope, and high-resolution transmission electron microscopic analysis. Archer *et al.*, (2020) reported that *Cassia sieberiana* is used traditionally for the treatment of several ailments. The lack of knowledge in the levels of essential mineral contents and heavy metal constituents of *C. sieberiana* normally collected from various sites for preparation of herbal products can pose serious health risks to consumers.

The elemental contents (Ca, Mg, K, Na, Cl, Hg, Pb, As, Ni, Cd, Cu, Fe, Mn, Zn, N, S and C) of a mixture of the stem and root barks (CSR) of *Cassia sieberiana* collected from Agomeda in the Eastern Region of Ghana and its extracts (absolute ethanol (CSE 1), 70% ethanol (CSE 2)) were investigated in the study. Preliminary phytochemical screening showed the presence of reducing sugar, saponins, polyphenols, anthracenosides and triterpenes in CSR, CSE 1 and CSE 2. The elements found in *Cassia sieberiana* and extracts are vital for human health. This contents indicate CSE 1 and CSE 2 may be suitable for use in drug formulation.

Napagoda *et al.*, (2018) reported that *C. auriculata* extract has displayed a strong tyrosinase inhibition with an IC₅₀ of 42.49 µg/mL, while the IC₅₀ value of the positive control (ascorbic acid) was determined as 33.70 µg/mL. The formulation developed from this extract has also displayed a potent inhibition of the enzyme with an IC₅₀ of 70.70 µg/mL which was extremely remarkable than the commercial preparation of kojic acid. In addition, *C. auriculata* extract has exhibited a strong antioxidant activity with an EC₅₀ value of 19.99 µg/mL, suggesting a possible correlation between tyrosinase inhibition and antioxidant activity. The preliminary findings reveal that *C. auriculata* has a high potential to be used as a natural skin whitening agent due to the inhibition of tyrosinase enzyme as well as the strong antioxidant activity.

Archer *et al.*, (2020) reported that, *Cassia sieberiana* is used traditionally for the treatment of several ailments. The lack of knowledge in the levels of essential mineral contents and heavy metal constituents of *C. sieberiana* normally collected from various sites for preparation of herbal products can pose serious health risks to consumers. The elemental contents (Ca, Mg, K, Na, Cl, Hg, Pb, As, Ni, Cd, Cu, Fe, Mn, Zn, N, S and C) of a mixture of the stem and root barks (CSR) of *Cassia sieberiana* collected from Agomeda in the Eastern Region of Ghana and its extracts were investigated in this study. For the purposes of identification and characterization of CSR, CSE 1 and CSE 2, FT-IR and phytochemical analyses were conducted. The quantity of metals in all test samples were within the acceptable WHO permissible limits except for Cl, Fe, Mn, Pb and Cd contents in CSR. It is mostly the extract of CSR which is consumed traditionally. The quantity of powdered CRS consumed during treatment of ailment may be too low to cause Cl, Fe, Mn, Pb and Cd toxicity.

FTIR studies showed similar functional groups in CSR, CSE 1 and CSE 2. Preliminary phytochemical screening showed the presence of reducing sugar, saponins, polyphenols, anthracenosides and triterpenes in CSR, CSE1 and CSE 2. The elements found in *Cassia sieberiana* and extracts are vital for human health. Their reported contents indicate CSE 1 and CSE 2 may be suitable for use in drug formulation.

Herbal cream-wound healing activity

Agyare *et al.*, (2016), was to determine the angiogenesis activity of *Jatropha curcas* latex in cream formulation on CD34 immune expression during wound healing phase in mice skin. Amount of 36 2-month-old male mice were used between 30 and 40 g. To surgical procedures, wound skin incision was performed 2.0 cm in length until subcutaneous on the para-vertebral of each animal. The treatment was carried under locally anesthetized with procaine cream.

All mice were divided into four groups, namely the base cream as control group (A), sulfadiazine 0.1% cream (B), *Jatropha curcas* latex cream 10% (C), and *J. curcas* latex cream 15% (D). All groups were treated entire surface of wound. These were performed twice a day for 10 days. Experiments were terminated on days 3, 7, and 10, respectively. The wound healing was assayed in stained histological section in immune histochemical of the wounds. It is showed that the cream from 10% and 15% latex *J. curcas* revealed moderate immune reaction to CD34 on days 3 and 7 in wound healing of mice skin. The cream from 10% and 15% latex *J. curcas* has potential as angiogenesis activity in wound healing of mice skin.

Skin is very sensitive and play vital role in sensing the environment, maintaining physicochemical and thermal homeostasis, acting as a reservoir of essential nutrients, providing passive and active defence, and responding to trauma and injury. The principal function expressed for the skin is to provide a protective barrier for the body against the surrounding environment (Singer and Clark, 1999). Loss of skin unity provides an appropriate context for various microorganisms to contaminate the wound surface (Bowler *et al.*, 2001). As intact skin is vital to protect the body against the environment, regenerative mechanisms (healing) need to be initiated and progressed to resolve the existing defect (Reynolds, 2001).

A term wound is defined as a break or cut break up in the integrity of the skin produced by a injuries and illness (Singh *et al.*, 2023). Wound is created by disease or accidental or intention reason (Velnar *et al.*, 2009). Wound is the shortest, minimal pain, discomfort and scarring to the patient and must occur in a physiologic environment conducive to tissue repair and regeneration (Bowler *et al.*, 2001). The healing properties of different plants species have contributed exceptionally to the derivation as well as the development of several traditional herbal medicines. Various plant species possess an assortment of phytochemicals, which have been applied in the fields of human medicine, agriculture and veterinary.

Cutaneous wound healing is the process by which skin repairs itself following injury caused by surgery, trauma and burns. Wound healing is the biological process repairing of tissue, regeneration of tissue act as network of blood vessels growth hormones and restoration of normal condition of the injured skin or tissue (Singer and Clark, 1999). Wound healing processes are known infections, nutritional status, drugs and hormones, type and sites of wound and wasting diseases like diabetes (Hannawa *et al.*, 2009).

Tirant *et al.*, (2018) studied to evaluate the multiherbal formulation PACT (containing extracts of *Pongamia pinnata* Linn., *Artocarpus lakoocha*, *Cynodondactylon* 27 Pers. and *Tridax procumbens* Linn.) for wound healing potential employing two common wound models i.e., excision wound and incision wound models. The wound contraction area and epithelialization period was measured in excision model while wound breaking strength and hydroxyproline contents were measured in incision wound model. The PACT significantly increased wound contraction, epithelialization, wound breaking strength and hydroxyproline contents when compared with control and the results were further supported by histopathological studies. This study concluded that this formulation exhibit potent wound healing efficacy in preclinical experiments and can further be studied for clinical purposes.

Kumar *et al.*, 2007 studied that the evaluation of *In vivo* wound healing activity of poly herbal formulation. Ointment of Arkaksheer, Snuhiksheer and combination of both will be evaluated for their wound healing activity in comparison with standard drug Soframycin ointment. The two models of wound healing have five groups (each group having six rats) the 5 groups are as follows. Group A of 6 wistar strain albino rats will be applied Ointment base twice a day. Group B of 6 wistar strain albino rats will be applied Ointment of ArkaKsheer Locally twice a day. Group C of 6 wistar strain albino rats will be applied Ointment of SnuhiKsheer locally twice a day. Group D of 6 wistar strain albino rats will be applied ointment of mixture of Arka, SnuhiKsheer locally twice a day. Group E of 6 wistar strain albino rats will be applied Soframycin ointment locally twice a day.

Khandekar *et al.*, (2007) demonstrated that an ethanol extract of *Lygodium flexuosum* leaves extract has properties that render it capable of promoting accelerated wound healing activity compared with the controls. The well-dried homogenous, free of dirt and foreign matter drug samples of leaves were subjected to grinding. In powder microscopy it was found that vessels are annular and thickened, trichomes are non-glandular multicellular it also shows the presence of pollen grains, calcium oxalate crystals and starch grains which are irregular ovoid, the fragments of cork, which are present to a greater extent; the cells are polygonal in surface view and have thin, lignified walls; the outer layers are filled with granular contents. The coarse powder of leaves of “*Lygodium flexuosum*” drug was successively extracted separately beginning with non-polar and gradually proceeding to polar solvents using soxhlet apparatus except in aqueous extraction.

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Chapter - 3

Breaking the Asthma Code: Overcoming Challenges, Embracing Benefits and Pioneering Drug Delivery Frontiers alongside Nutraceutical Innovations

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Chapter - 3

Breaking the Asthma Code: Overcoming Challenges, Embracing Benefits and Pioneering Drug Delivery Frontiers alongside Nutraceutical Innovations

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Abstract

This article discusses the challenges in drug delivery and the potential benefits of Chronomodulated drug delivery for antiasthmatic drugs. It explores new drugs, personalized medicine approaches, and future directions in asthma treatment, such as immunotherapy and gene therapy. The analysis also discusses the risks of gene therapy for severe asthma and its potential benefits, such as improved medication effectiveness and reduced side effects. Chronomodulated drug delivery, which involves administering medications at specific times to align with the body's natural rhythms, has shown promising results in improving asthma control and reducing the frequency and severity of attacks. For instance, a study found that administering a Chronomodulated antiasthmatic drug in the morning, when lung function is typically at its lowest, significantly improved drug absorption and bioavailability compared to regular drug delivery. This optimized drug delivery not only enhanced the medication's effectiveness but also reduced the need for frequent dosing and minimized side effects, leading to better overall asthma management.

Keywords: Asthma, drug delivery, nutraceuticals, management, patient

Introduction

In order to control asthma and enhance patient outcomes, medication delivery must be done effectively. Delivering asthma medications presents a number of challenges, including new research, technology, and the need for ongoing improvements. Addressing the complicated difficulties of asthma management requires a multidisciplinary strategy combining researchers, policymakers, and healthcare practitioners ^[1]. Patient education and empowerment are essential for ensuring effective drug delivery and enhancing the quality of life for individuals with asthma. Smart inhalers,

equipped with sensors and connectivity features, track medication usage and send real-time data to healthcare professionals, researchers, and policymakers. This technology enables better understanding of patient adherence, triggers and treatment effectiveness, leading to tailored interventions and improved asthma management strategies. Healthcare professionals can educate patients on proper inhaler technique, ensuring the medication is delivered effectively to the lungs. However, if a patient is well-educated on proper inhaler technique but still experiences poor asthma management, personalized treatment plans that address individual factors and provide tailored solutions are necessary. These personalized treatment plans may involve adjusting medication dosages, exploring alternative medications, or identifying and addressing triggers that worsen asthma symptoms ^[2-4]. Additionally, healthcare professionals can collaborate with patients to develop self-management strategies, such as creating an asthma action plan and regularly monitoring symptoms, to further improve asthma management outcomes ^[5]. In addition to highlighting the value of technology in tracking and monitoring asthma, the user also highlights the necessity of individualized treatment strategies that go beyond what technology can provide.

They provide examples of tailored solutions for individual factors in asthma management, such as specialized inhalers or allergen-specific immunotherapy, which can improve overall asthma control and reduce the risk of severe attacks ^[6]. Healthcare professionals should actively involve patients in the decision-making process, considering their preferences and lifestyle factors. This collaborative approach ensures that treatment plans are effective and sustainable in the long term. The user emphasizes the importance of ongoing education and support for patients, empowering them to take an active role in managing their asthma and making informed choices about treatment options ^[7]. Together, patients and healthcare providers can develop a customized treatment plan that takes into account the patient's preferences and lifestyle aspects, including daily schedule, medication preferences, and non-pharmacological interventions like food modifications or breathing exercises. By giving patients the information and resources they need to properly manage their asthma on a daily basis, this method lowers the need for emergency care and enhances the patients' quality of life in general. Nonetheless, a patient who is uncooperative with pharmaceutical regimens or lifestyle modifications could serve as a counterexample to this strategy. Even with the best efforts of the healthcare professional, the patient may still fail to take care of their asthma, which could result in frequent flare-ups and trips to the emergency room. For many patients, education and

support might be beneficial, but there will always be those people who are unwilling to make [8]. These individuals may have various reasons for their resistance, such as a lack of understanding about the importance of asthma Journal Pre-proof management or a fear of side effects from medication. It is crucial for healthcare professionals to continue providing education and support, while also exploring alternative approaches or interventions that may better suit the needs and concerns of these resistant patients.

Overview of antiasthmatic drugs and their current delivery methods

The difficulties people have daily in controlling their asthma are highlighted by the user's input. Healthcare providers are better able to customize treatment regimens to each patient's requirements when they are knowledgeable about the various antiasthmatic medication types and how they are delivered.

Exploring the impact of environmental factors, such as air pollution and allergens, can help identify triggers and develop strategies to minimize their effects on asthma symptoms [9, 10]. Healthcare professionals also play a crucial role in educating patients about their condition and providing ongoing support for proper self-management. Strategies to improve medication adherence, such as reminder systems and patient education programmes, can further enhance asthma control [11-13]. Public health initiatives can reduce overall air pollution levels and improve air quality, benefiting not only individuals with asthma but the general population. Implementing stricter emissions standards for factories and vehicles and creating green spaces in urban areas can promote the growth of plants that naturally filter pollutants from the air, providing a cleaner environment this can significantly mitigate the impact of environmental triggers on asthma symptoms [14, 15]. However, these measures do not guarantee complete elimination of environmental triggers for asthma. Highly polluted areas may still experience asthma symptoms despite stricter emissions standards and green spaces hence, more effective methods of reducing air pollution are need to develop. Furthermore, the implementation of education and awareness initiatives can assist people in realizing the significance of upholding a hygienic environment and adopting the appropriate safety measures to treat asthma symptoms in urban settings.

Conventional drug delivery systems and their mechanisms

Chronomodulated drug delivery systems are a growing field of research that focuses on targeting affected tissues or cells to minimize side effects and maximize therapeutic effects. Current advancements in this field include the

use of nanoparticles or liposomes, as well as stimuli responsive systems that release drugs in response to specific triggers ^[16]. These advancements have the potential to revolutionize medicine by providing more precise and effective treatment options. Researchers have developed nanoparticles coated with antibodies that target tumor cells, minimizing damage to healthy cells and reducing side effects. In diabetes management, insulin can be encapsulated within liposomes that only release the drug when glucose levels reach a certain threshold, providing precise control over insulin delivery ^[17]. This approach not only improves treatment effectiveness and reduces toxic effects on surrounding healthy tissues. However, challenges in implementing nanotechnology-based drug delivery systems on a large scale remain. High manufacturing costs and complexity of scaling up production hinder widespread use, making them inaccessible for many patients in need. Concerns about potential long-term side effects and limited knowledge about nanoparticles' environmental impact raise ethical and safety concerns ^[18]. However, advancements in technology and research can potentially overcome these challenges, leading to reduced manufacturing costs and improved scalability. Furthermore, thorough investigation and testing can guarantee the safety and moral feasibility of nanotechnology-based medicine delivery systems by offering a deeper comprehension of their long-term impacts. In addition, rules and regulations can be set up to keep an eye on the creation and application of nanoparticles, guaranteeing ethical and sustainable behavior. In order to allay any worries or disbeliefs regarding nanotechnology and promote acceptance and confidence in its uses, public awareness and education campaigns can also be extremely important.

Discussion on different types of conventional drug delivery systems

The economic implications of adopting nanotechnology in pharmaceutical manufacturing processes, focusing on the potential benefits and advancements offered by nanotechnology in personalized medicine ^[19-24]. The input acknowledges regulatory challenges and ethical considerations associated with the use of nanotechnology-based drug delivery systems. The economic implications of adopting nanotechnology in drug delivery include potential cost savings and increased efficiency in the healthcare industry. One challenge associated with nanotechnology-based drug delivery systems is the potential for unintended side effects or toxicity ^[25, 26]. If nanoparticles are not properly designed or tested, they could accumulate in certain organs or tissues, causing harm to the patient. Additionally, ethical considerations arise when determining who should have access to these advanced drug delivery systems, as they may be more expensive and not readily available to

all patients. The successful use of liposomal doxorubicin in cancer treatment has demonstrated the potential of nanotechnology-based drug delivery systems in improving patient outcomes and reducing side effects compared to traditional chemotherapy. However, the potential development of drug resistance in cancer cells over time may render the targeted delivery system ineffective. It is imperative to advocate for the fair distribution and cost-effectiveness of liposomal doxorubicin; nevertheless, it is also critical to acknowledge that drug resistance in cancer cells may emerge, which could diminish the efficiency of this targeted delivery method and restrict its benefits for all patients. To address the issue of drug resistance, ongoing research is focused on developing combination therapies that can overcome or delay its development. By combining liposomal doxorubicin with other drugs or treatment modalities, we can potentially enhance its efficacy and prolong its effectiveness in treating cancer. Additionally, continuous monitoring and surveillance of patients receiving liposomal doxorubicin can help identify any signs of drug resistance early on, allowing for timely intervention and adjustment of treatment strategies.

Advantages and limitations of conventional drug delivery systems

Cancer cells can develop resistance to liposomal doxorubicin through various mechanisms, including overexpression of drug efflux pumps like P-glycoprotein, up regulation of DNA repair mechanisms, and alteration of drug target molecules like topoisomerase II. These changes can reduce the drug's effectiveness in killing cancer cells and contribute to treatment resistance. However, not all cancer cells develop resistance through alterations in drug target molecules. In some cases, resistance can also occur due to the presence of cancer stem cells, which have unique properties that make them difficult to eradicate with traditional treatments. Targeting only drug Journal Pre-proof target molecules may not be sufficient in overcoming treatment resistance in certain types of cancer, but focusing solely on drug target molecules may still be effective in treating many types of cancer that do not involve cancer stem cells. Successful treatment outcomes may result from the development of tailored treatments for these particular molecules. Additionally, creating successful treatments requires an understanding of the signaling pathways and mechanisms that support cancer stem cells' ability to survive and proliferate. By targeting these specific pathways, it may be possible to disrupt the maintenance and growth of cancer stem cells, ultimately improving treatment outcomes for patients with resistant cancers [27-30].

Overview of commonly used antiasthmatic drugs

The user's input provides a comprehensive overview of antiasthmatic drugs, analyzing mechanisms of action, effectiveness, and side effects. It also discusses the exploration of new drugs, personalized medicine approaches, and potential future directions in antiasthmatic drug research, including immunotherapy and gene therapy. Asthma is a chronic respiratory condition affecting millions of people worldwide, causing symptoms like wheezing, shortness of breath, and chest tightness ^[31]. Current antiasthmatic drugs have been effective in controlling symptoms, but there is still a need for more targeted and effective therapies. Researchers are studying monoclonal antibodies as a potential treatment for severe asthma, targeting and blocking proteins involved in triggering attacks. Advancements in gene therapy offer the potential to modify the genetic makeup of asthmatic individuals, potentially reducing susceptibility to attacks and minimizing long-term medication use. However, the development of resistance to monoclonal antibodies in some asthmatic patients could render the treatment ineffective over time. Additionally, gene therapy may carry the risk of unintended consequences or unforeseen side effects, raising concerns about its long-term safety and efficacy in treating severe asthma. Despite the potential benefits, it is important to consider the ethical implications of genetic modification in asthma treatment. Questions arise regarding the accessibility and affordability of such therapies, as well as the potential for unequal distribution of benefits among different populations. Furthermore, extensive research and clinical trials are necessary to ensure the safety and effectiveness of gene therapy before it can be widely implemented as a treatment option for severe asthma.

Discussion on the pharmacokinetics and pharmacodynamics of antiasthmatic drugs: The user seeks a comprehensive understanding of asthma treatment options and the potential of gene therapy as a game-changing intervention. They aim to identify gaps in knowledge and areas that require further investigation, as well as gain insights into the practicality and feasibility of implementing gene therapy as a mainstream treatment for severe asthma ^[21]. One potential approach is to investigate the efficacy of gene therapy in targeting specific antibodies implicated in severe asthma. They can analyse how introducing modified genes into the respiratory system can alter the production and function of these antibodies, potentially reducing inflammation and improving respiratory function in patients. The user also aims to determine the safety and long-term effects of gene therapy-based treatments for severe asthma. However, a study involving modified

genes in animal models with severe asthma showed that gene therapy could actually lead to increased inflammation and worsened respiratory function, raising concerns about its safety and effectiveness. The user aims to contribute to the existing body of knowledge and pave the way for future advancements in asthma management. By conducting this study, the user hopes to address the limitations of previous research and provide valuable insights into the potential risks and benefits of gene therapy for severe asthma. This research could ultimately help inform clinical decision-making and improve patient outcomes in the field of asthma treatment.

Current challenges in drug delivery and potential benefits of Conventional drug delivery for antiasthmatic drugs

Further research is needed to understand the mechanisms of increased inflammation and worsened respiratory function in animal models with severe asthma. Alternative treatment options, such as immunotherapy or targeted biologic medications, may offer better safety and effectiveness profiles. Animal models may have limitations in accurately predicting human response to gene therapy for severe asthma, highlighting the importance of conducting clinical trials in humans. Ethical considerations surrounding gene therapy for severe asthma in animal models include potential harm to animals and the need for strict regulations and guidelines ^[21]. Clinical trials play a vital role in determining the safety and efficacy of gene therapy for severe asthma in humans. Pre-proofing the Journal Through these trials, researchers can keep a close eye on how gene therapy is working for patients, reducing the possibility of side effects and maximising the therapy's ability to reduce asthma symptoms. To safeguard the rights and welfare of trial participants, stringent laws and moral standards must be established. To administer gene therapy, for instance, researchers might enlist a group of individuals with severe asthma who have not reacted well to conventional treatments. This detailed analysis would help determine the safety and effectiveness of the treatment, allowing informed decisions about its future use in asthma management. However, a potential counterexample could be seen if the gene therapy results in severe adverse effects or worsens asthma symptoms, highlighting the need for further investigation and caution before considering the treatment as a viable option for asthma management. Additionally, it is important to consider the long-term effects of gene therapy on patients and whether any potential benefits outweigh the risks. Furthermore, conducting clinical trials with a larger sample size and diverse population would provide more comprehensive data on the treatment's efficacy and safety profile in different asthma subtypes.

Review of studies and research on conventional drug delivery of antiasthmatic

Chronomodulated drug delivery has the potential to improve asthma management by optimizing medication efficacy and reducing side effects. However, challenges in implementing this approach include variability in individual circadian rhythms, which can make it difficult to accurately time drug delivery based on these rhythms. Additionally, the integration of wearable technology for real-time monitoring and adjustment poses challenges, such as the development of reliable and accurate sensors and user-friendly interfaces. Ensuring privacy and security of patient data collected through wearable technology is also a key consideration. For instance, wearable insulin pumps for diabetic patients can deliver insulin based on glucose levels, but if irregular sleep patterns or disrupted circadian rhythms, accurate timing can be difficult. Ensuring that data collected by these devices is secure and protected from unauthorized access is vital to maintain patient privacy ^[27]. A counterargument is that insulin pumps are highly regulated and undergo rigorous testing before being approved for use, reducing the likelihood of malfunctions. Advancements in cybersecurity measures can help protect patient data and minimize the risk of unauthorized access or misuse. Overall, further research and development are needed to fully harness the potential of Chronomodulated drug delivery for asthma management. In addition, it is Journal Pre-proof important to consider the potential benefits of Chronomodulated drug delivery for asthma management, such as improved medication effectiveness and reduced side effects. However, it is crucial to address any concerns regarding patient privacy and ensure that robust cybersecurity measures are in place to safeguard sensitive medical information.

Nutraceutical management

Bronchial asthma: The use of patented products to treat physiological issues, focusing primarily on the interaction between several medications, for bio prospecting analysis and the discovery of new bioactive mixtures from common sources, has been extensively reported with ethnopharmacological attention. These from specific attribute sources provide considerable contributions to the discovery of new therapeutic pharmaceuticals and their improvement, despite the enormous logical development regarding artificial and drug innovation on combining new tablets and atoms. Because they are practical and simple to use, drug agencies give corporations permission to conduct multiple studies that examine the therapeutic benefits, toxicity, and safety of many common things used in generic form ^[32-34].

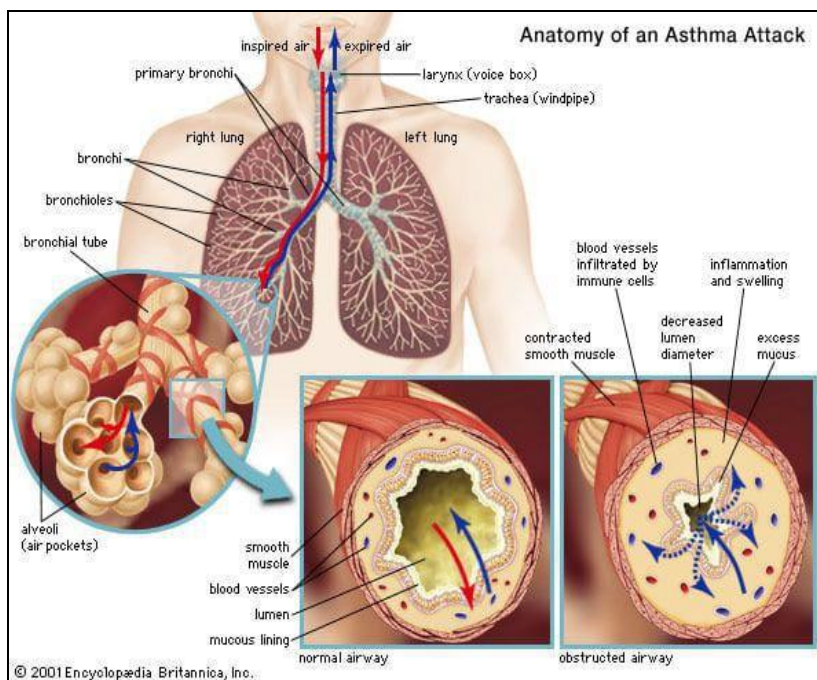










Fig 1.1: Bronchial asthma






Around 40% of a common cure in the United States of America is addressed by the use of everyday goods, nutrients, and additional dietary modifications as assistant pharmaceuticals. People with negative personality traits and fiery dispositions might wish to be exposed to the viruses that commonplace devices use. In fact, as the literature has revealed, the use of these items with biochemical structures involved in immunomodulation should be added to the management of these diseases. Since more than 5000 years ago, products based on flora have been used as a common therapy for bronchial asthma. Their use is linked to Chinese lifestyles that were developed as a result of the imbue ment of Ephedra silica as a safe form that started off organised to decrease bronchial asthma crises the study focused on beet, honey, garlic, yarrow, onion, lemon, and mint, showcasing the range of characteristic objects used in children's bronchial asthma treatment. Additionally, other commonly deduced substances have also been widely mentioned in the bronchial asthma treatment, such as common oils derived from plants and animals that can be concentrated to a smaller volume. Plant-based oils are often used in reciprocal bronchial asthma treatments. Because of mixes, such as the most bioactive combinations of phenylpropanoids and mono and sesquiterpenes, which have sedative, antifungal, relieving, and






antibacterial qualities, the major common goods are utilized. Elevate endogenous adrenal cortex steroid levels as soon as possible. This includes reducing bodily fluid entrance and aggravation in lung tissues when combined with the NF- κ B pathway's guiding principle. Additionally, it has been found that a number of minerals guard against respiratory conditions ^[35-37]. Increased consumption of magnesium, calcium, and potassium in children is negatively correlated with asthma prevalence. A controlled trial found that a low-sodium diet did not improve bronchial responsiveness in individuals with asthma, despite the contradictory results of other observational and experimental investigations. Dietary magnesium supplementation may have advantageous bronchodilator effects in asthmatic patients. Reduced lung function in children and negative effects on bronchial smooth muscle in individuals with severe asthma have both been associated with low dietary magnesium intake. Further evidence of positive therapeutic effects is required before its importance in asthma and recommendations can be made. It has been shown that individuals with asthma consume less selenium through diet than people without the condition, and there is a negative correlation between maternal plasma selenium levels and asthma symptoms.





Table 1.1: List of Nutraceutical agents used in the management of asthma




S. No.	Name of the drug	Image	Biological source	Family	Chemical constituents	Uses
1.	Beetroot		<i>Beta vulgaris</i>	Amaranthaceae	Syringic acid, P-Coumaric acid, Betanin, Oleanolic acid, Indicaxanthin	Regulate blood pressure, prevent anemia, help to fight against inflammation
2.	Garlic		<i>Allium sativum</i>	Amaryllidaceae	Allicin, Alliin, Ajoene, Diallyl disulfide, Diallyl trisulfide.	Prevent heart disease, Anti- inflammatory, prevent cold
3.	Lemon		<i>Citrus lemon</i>	Rutaceae	Oil, Limonene, Myrcene, Nerol, Citric acid.	Helps Prevent Asthma, Increase Iron absorption, Helps Fight Cancer
4.	Mint		<i>Fresh or dried leaves</i>	Lamiaceae	Menthol, Menthone, Elemene, Limonene, Menthyl acetate	Improved digestive health, boost your immune system, Reduce cold symptoms.

5.	Yarrow		<i>Achillea millefolium</i>	Asteraceae	Eucalyptol, Borneol, Centaureidin, Casticin	Help to treat Muscle spasms, Inflammation, to fight against infection.
6.	Brahmi ^[55]		<i>Bacopa monnieri</i>	scrophulariaceae	Bacosides, Iotiolide	As antioxidants, reduce inflammation, boost brain function, prevent anxiety, stress
7.	Blue flowered glory tree ^[47]		<i>Clerodendrum serratum</i>	Verbenaceae	D-mannitol, Hispidin, Oleanolic acid	Used in the treatment of common cold, chronic sinusitis, allergic rhinitis, cough.
8.	Monnier's snowparsley ^[38]		<i>cnidum monnieri</i>	Umbelliferae	Osthale	Help to boost the immune system, improve circulation, reduce inflammation, reduce fatigue, improve skin health.

9	Eclipta alba ^[42]		<i>Eclipta prustrata</i>	Asteraceae	Demethylwedelactone, Wedolactone, Ecliptal	Used to treat snake bite, wounds and prevent hairloss.
10	Banayan tree ^[44, 45]		<i>Ficus bengalensis</i>	Moraceae	Steroids, flavonoids, Tannins	Antioxidant, treat Arthritis, Diabetes and Enhances skin health, Prevent Inflammation.
11.	Indian sarsaparilla ^[47]		<i>Hemidesmus indicus</i>	Apocynaceae	Lupeol, Amyrin	Used to treat rheumatism, leprosy, impotence, urinary tract and skin infections.
12	Ginger		<i>Zingiber officinale</i>	Zingiberaceae	Gingerol, shogaol	Calms Nausea, Soothes Sore Muscles, Eases Arthritis Symptoms, Curbs Cancer Growth, Lowers Blood Sugar.
13	Garden cress ^[50]		<i>Lepidium sativum</i>	Brassicaceae	Alkoids, flavonids, saponin	Treatment of hyperactive airways disorders, such as asthma, bronchitis and cough.

14	Spearmint ^[51]		<i>Mentha spicata</i>	Lamiaceae	Flavonids, glycosides	Treatment of cold, cough, asthma, fever, obesity, jaundice and digestive problems.
15	Spiny gourd ^[52]		<i>Momordica dioica</i>	Cucurbitaceae	Alkoids, flavonoids, glycosides	Remedy for diabetes mellitus, Lower risk of chronic diseases, Prevent cardiovascular disease.
16	Olive ^[46]		<i>Olea euphorbia</i>	Oleaceae	Secoiridoid, Tyrosol	Used as a laxative, antiseptic, astringent, helps to treat peptic ulcer.
17.	Betel leaves ^[40]		<i>Piper betel</i>	Piperaceae	Charicol, chavibetol, eugenol	Antioxidant, Antidiabetic, Reduce inflammation, Treat respiratory catarrhs.
18.	Night Blomming Jasmine ^[49]		<i>Nyctanthes arbortristis</i>	Oleaceae	Astragaline, Sitosterol, Nicotiflorin	In homeopathy treat various disorders related to stomach, head.

19.	Bayberry ^[53]		<i>Myrica esculenta</i>	Myricaceae	Tannins, Terpenes	Relief cough, ulcer, inflammation, anemia
20.	Cerejeira ^[48]		<i>Amburana cearensis</i>	Fabaceae	Flavonoid, isokaempferide	Folk medicine as teas, decocts
21.	Asthma plant ^[43]		<i>Euphorbia hirta</i>	Euphorbiaceae	Triterpenes, polphenols	Used in worm infestation in Children, jaundice, gonorrhea.
22.	Coromandel ^[57]		<i>Asytasia gangetica</i>	Acanthaceae	Saponins, terpenoids	Roots as powder used in snakebite, stomach ache and leaf for treatment in urethral discharge.

23.	Senna sophera ^[56]		<i>Cassia sophera</i>	Caesalpinaceae	Dihydro ascorbic acid	Homeopathy remedy in treatment of ringworm infection.
24.	String lilly ^[39]		<i>Crinum glaucum</i>	Amaryllidaceae	Tazattine, zeylamine	Treatment of microbial infection, sexually transmitted diseases.
25.	Kali musli ^[41]		<i>Curculigo orchoides</i>	Amaryllidaceae	Sterols, Lycorine, Sitosterol	Treatment of limpness, watery diarrhea and aphrodisiac in ayurvedic system.

Conclusion

The development of targeted drug delivery systems has been facilitated by the introduction of nanotechnology. The problems with drug delivery today and the possible advantages of chronomodulated drug delivery for antiasthmatic medications are the main topics of this review. The examination covers novel medication development, personalised medicine strategies, and prospective avenues for asthma treatment going forward, such as gene therapy and immunotherapy. It also examines the advantages and disadvantages of gene therapy for severe asthma, including increased drug efficacy and decreased side effects. This review discussed the list of nutraceutical products used to treat, manage or prevent the bronchial asthma.

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Chapter - 4

Role of Flavonoids in Inflammatory Bowel Disease

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Chapter - 4

Role of Flavonoids in Inflammatory Bowel Disease

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Abstract

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract with a multifaceted etiology involving genetic, environmental, and immunological factors. While conventional treatments primarily focus on managing inflammation and symptoms, their long-term use often leads to significant side effects, prompting a search for alternative therapies. Flavonoids, a diverse group of polyphenolic compounds found in fruits, vegetables, and other plant-based foods, have emerged as potential therapeutic agents due to their anti-inflammatory, antioxidant, and immunomodulatory properties. This chapter explores the role of flavonoids in the management of IBD, detailing their mechanisms of action, including the inhibition of key inflammatory signaling pathways, reduction of oxidative stress, modulation of gut microbiota, and regulation of immune responses. Preclinical studies demonstrate the efficacy of various flavonoids in animal models of IBD, while clinical trials present mixed but promising results. Practical considerations for dietary incorporation and supplementation of flavonoids are discussed, along with future research directions aimed at optimizing their therapeutic potential. Integrating flavonoid-rich foods into a balanced diet may offer a natural and holistic approach to support the management of IBD, highlighting the need for further research to establish comprehensive guidelines for their use in clinical practice.

Keywords: Gastrointestinal, flavonoids, anti-inflammatory, IBD

Introduction

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract. The exact etiology of IBD remains unclear, but it involves a complex interplay of genetic, environmental, and immunological

factors ^[1]. Current treatment strategies primarily focus on reducing inflammation and managing symptoms through pharmacological and surgical interventions. However, these treatments often come with significant side effects and do not offer a cure. As such, there is a growing interest in alternative and complementary therapies, including dietary interventions. Among these, flavonoids, a diverse group of phytonutrients found in fruits, vegetables, and other plant-based foods, have garnered significant attention for their potential anti-inflammatory and immunomodulatory effects ^[2].

At present, the etiology of IBD is not fully understood, and many theories have been proposed to explain IBD pathogenesis, ranging from infectious to psychosomatic, social, metabolic, vascular, genetic, allergic, autoimmune and immune-mediated mechanisms ^[3, 4, 5]. Currently, there is a general agreement that IBD occurs in genetically predisposed subjects who exhibit a dysfunctional intestinal epithelium barrier with increased tight junction permeability. In these conditions, these patients develop an exaggerated immune response in the gut towards the intestinal microbiota, which is not conveniently controlled and leads to chronic intestinal inflammation ^[3].

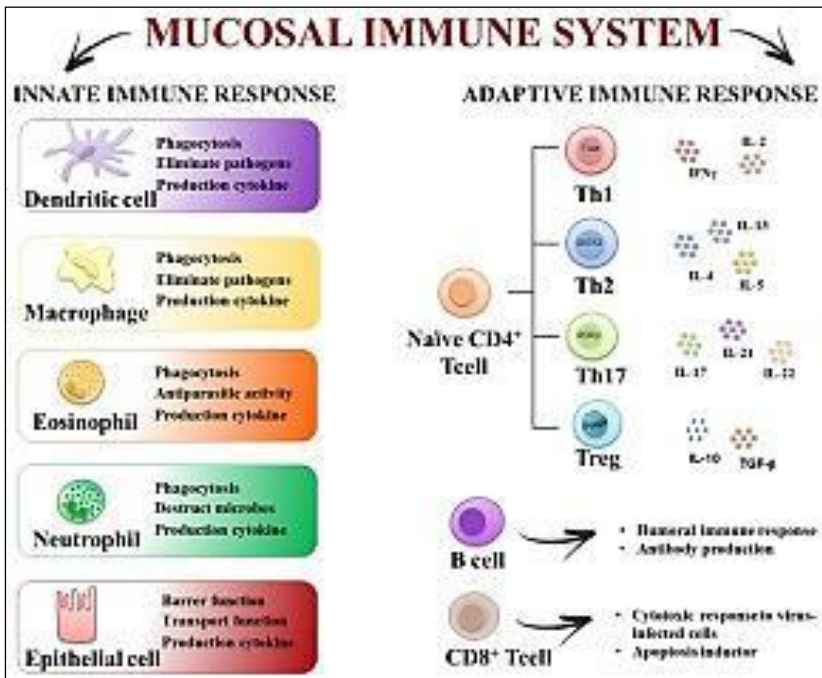


Fig 1: The mucosal immune system constitutes a key element in preventing penetration of microorganisms. It consists of innate and adaptive immune responses. The innate immune response is the first line of defense against infection and includes complement proteins, granulocytes (basophils, eosinophils and neutrophils), mast cells, macrophages, dendritic cells and natural killer cells. The adaptive immune response develops more slowly, but it is manifested as increased antigenic specificity and memory. It consists of antibodies, B cells, and CD4⁺ and CD8⁺ T lymphocytes.

Disruption of the innate and acquired gut immune systems may cause the development of chronic intestinal diseases

In fact, various components of the mucosal immune system in the gut have been implicated in the pathogenesis of IBD. They include elements of the innate immune system such as intestinal epithelial cells, macrophages/monocytes, neutrophils, dendritic cells (DCs), as well as constituents of the adaptive immune system such as T-cells and B-cells as well as their secreted mediators (cytokines and chemokines) (Figure 1). It has been proposed that an initial defect in sampling gut luminal antigens, or a mucosal susceptibility, leads to the activation of the innate immune response, most probably associated with an enhanced Toll-like Receptor (TLR) activity. Then, antigen-presenting cells (APCs) can mediate the differentiation of naïve T-cells into effector T helper (Th) cells, including Th1, Th2, and Th17 cell types, and macrophage proliferation, thus impairing

the immune tolerance to commensal bacteria in the intestine ^[6]. In consequence, there is an abnormal synthesis and release of different pro-inflammatory mediators, including eicosanoids, platelet-activating factor, cytokines and reactive oxygen and nitrogen metabolites, which lead to the mucosal damage and the generation of a vicious circle that sustains the inflammatory response that characterizes human IBD ^[7, 8, 9].

Nowadays, and since the precise etiology of IBD is unknown, there is no specific causal treatment for these intestinal conditions. For this reason, the main goals of IBD therapy are, firstly, to induce the remission of the symptoms during the acute flare, and secondly, to preserve the remission by controlling the chronic inflammation, thus preventing the reactivation of the intestinal inflammatory process. With these aims, one of the main strategies to effectively counteract the exacerbated immune response is to interfere with multiple stages of the inflammatory cascade, mainly by using aminosalicylates (sulfasalazine or mesalazine), immunosuppressants (glucocorticoids, azathioprine, methotrexate, and cyclosporine A), and biologicals (infliximab or adalimumab) ^[10]. Unfortunately, these treatments are not devoid of potentially serious side effects, thus limiting their chronic use ^[11]. In consequence, there is a clear demand for safe and effective therapeutic strategies for human IBD. This could be the case for flavonoids, natural phenolic products that are found in edible fruit and vegetables and present several biological activities, mainly related to their antioxidant properties and ability to inhibit enzymes, which justify their reported capacity to downregulate the immune response ^[12]. Therefore, they could be taken into consideration as potential drugs for the pharmacological treatment of IBD. The aim of this review is to provide scientific arguments that would support the use of flavonoids in the treatment of human IBD, based on different studies that have shown the efficacy of these compounds both in clinical trials and in an experimental model of rodent colitis. Moreover, we will analyze the mechanisms that may be involved in their beneficial effects in these intestinal conditions. With this purpose we will focus on the most relevant groups of flavonoids with demonstrated intestinal anti-inflammatory properties: anthocyanidins, catechins, chalcones, flavanones, flavones, flavonols, isoflavones.

Antioxidant properties of flavonoids

Several studies have proposed that both ROS and RNS also play a key role in the etiology of IBD ^[13]. In fact, human IBD has been associated with an intense oxidative stress, excessive generation of ROS and RNS in the intestinal tissue which induces lipid peroxidation, protein modifications,

DNA damage, and apoptosis, together with impairment of the enzymatic and non-enzymatic antioxidant mechanisms, including superoxide dismutase (SOD), and reduced glutathione (GSH) and catalase (CAT), which results in the colonic damage associated with intestinal inflammation ^[14, 15]. Different sources of free radicals have been proposed to contribute to the oxidative burst that takes place in IBD, with neutrophils among the cells most involved in these processes ^[16]. The infiltration of polymorphonuclear neutrophils and mononuclear cells into the affected part of the intestine is considered one of the main pathological features of human IBD ^[17]. As a consequence of the activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system in these cells, and the subsequent myeloperoxidase activity (MPO), massive quantities of superoxide and hypochlorous acid are generated and cause direct cytotoxicity in the intestinal tissue. This, in turn, facilitates the additional release of different pro-inflammatory mediators ^[18]. In fact, most flavonoids assayed in experimental colitis models exhibited a significant reduction of colonic myeloperoxidase. This enzyme is predominantly found in the azurophilic granules of the neutrophils and is considered to be a sensitive marker of leukocyte infiltration ^[19]. As expected, MPO activity is increased in different experimental models of colitis induced by TNBS, DSS and T cell transfer. The increased MPO levels were significantly reduced after the administration of genistein and quercitrin in the TNBS model ^[20, 21]. A similar effect was induced by quercitrin as well as with cardamomin, chrysin, EGCG, naringenin and rutin in the DSS model ^[22, 23, 24, 25, 26, 27, 28]. Finally, it is important to remark that rutin administration was also able to reduce leukocyte infiltration in the T cell transfer model ^[29].

Most of the flavonoids assayed were able to ameliorate the oxidative stress that takes place in the experimental models of colitis as evidenced by a reduced colonic lipid peroxidation, together with an improvement in different antioxidant markers, including sulfhydryl-derived compounds, or an enhancement of different enzyme activities with antioxidant properties ^[28]. Specifically, several studies have suggested that both EGCG and quercitrin administration on the DSS-induced colitis model were able to increase the colonic GSH production, and naringenin and EGCG reduced the tissue malondialdehyde (MDA) levels, indicating both a reduction of lipid peroxidation and an increase of antioxidant enzymes such as SOD and GPO ^[24, 25, 27, 30]. Similarly, quercitrin and rutin treatment have shown to significantly increase GSH levels, thus ameliorating the colonic damage in the TNBS model ^[30].

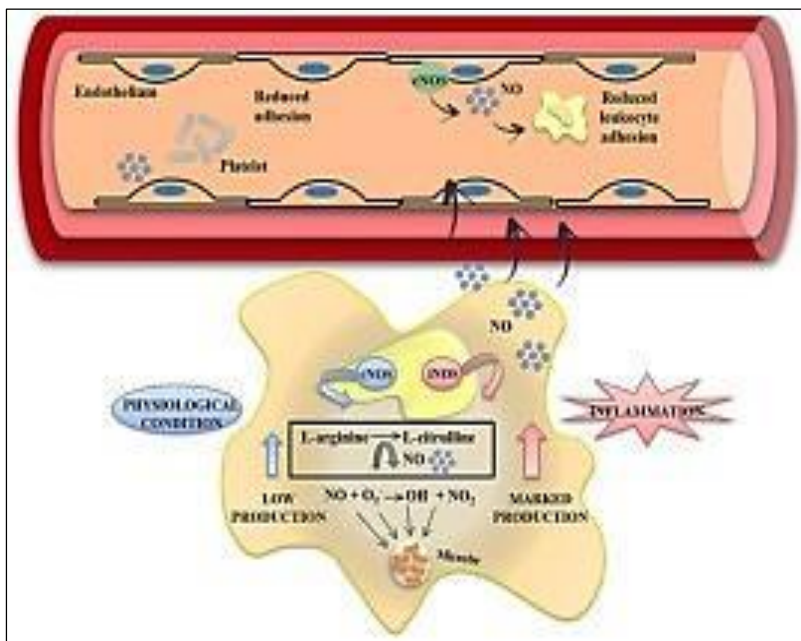


Fig 3: Nitrite oxide (NO) is a free radical molecule generated from L-arginine oxidation, and is catalyzed by the enzyme nitric oxide synthase (NOS). Different functional forms of NOS can be recognized: constitutive and inducible forms. NO synthesis by the constitutive isoform, endothelial NOS (eNOS), generates low levels of NO under normal physiological conditions which regulates the colon blood flow, bowel motility and produces reactive oxygen species (ROS) for fighting pathogens. The inducible isoform, iNOS, is expressed in cells involved in the inflammatory response and, upon different stimuli, generates high levels of NO that may be toxic to the healthy tissue, contributing to damage and upregulation of the inflammatory response. Several studies clearly demonstrated that certain flavonoids inhibit NO production in activated cells and in induced experimental colitis. Their inhibitory activity might be due to reduction of iNOS enzyme expression.

Special attention can be paid to the RNS, which can be produced and released by immune cells and also play an important role in the pathophysiology of IBD. Nitric oxide (NO) is a pleiotropic free radical messenger molecule produced from L-arginine by the nitric oxide synthase (NOS) enzyme. Under physiological conditions, low levels of NO are produced by the isoform of constitutive nitric oxide synthase (cNOS), which has a direct protective effect throughout the initial phases of the intestinal inflammatory process. Nevertheless, in chronic inflammation, NO synthesis is upregulated, mainly as a consequence of the increased expression of the inducible isoform of nitric oxide synthase (iNOS), which is induced, mainly

in macrophages, by bacterial products and pro-inflammatory cytokines ^[30, 31]. The overproduction of NO contributes to colonic damage due to its interaction with the superoxide anions, thus generating peroxynitrites, which reinforce oxidative stress and tissue damage ^[32] (Figure 2). Numerous studies have described an effect of flavonoids on the metabolism of NO, which may preserve the beneficial functions of NO through the direct capture of superoxide anions ^[33]. Similarly, it has been reported that flavonoids are capable of inhibiting the expression of iNOS ^[34] as well as acting as powerful captors of peroxynitrite radicals ^[35]. Moreover, DSS administration is associated with a significant increase of iNOS. In this regard, it has been observed that some flavonoids such as glabridin, cardamonin, naringenin and quercitrin improve the inflammatory process, reducing the expression of iNOS and, as a consequence, the NO production ^[22, 23, 24, 27]. These results have been confirmed in *in vitro* studies with different cell lines. EGCG, naringenin, daidzenin, kaempferol, quercetin and cardamonin inhibit iNOS protein and mRNA expression and also NO production in lipopolysaccharide (LPS)-activated macrophages, such as bone marrow-derived macrophages (BMDM), or murine macrophages J774 and mouse leukemic monocyte macrophage (RAW 264.7) cell lines ^[26, 27, 29, 33]. Flavonoids are capable, therefore, of preventing the detrimental effects generated by NO in intestinal inflammation.

Understanding flavonoids

Flavonoids are a large class of polyphenolic compounds that are ubiquitously present in the plant kingdom. They can be classified into several subgroups, including flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanins. Each subgroup has distinct structural characteristics and biological activities. The primary sources of flavonoids include:

Flavonols: Found in onions, kale, and apples.

Flavones: Present in parsley, thyme, and celery.

Flavanones: Found in citrus fruits.

Flavanols: Present in tea, grapes, and berries.

Isoflavones: Found in soybeans and other legumes.

Anthocyanins: Present in berries, red cabbage, and red wine.

Flavonoids exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antiviral, and anticancer properties. These

effects are primarily attributed to their ability to modulate various cellular signaling pathways and gene expression.

Mechanisms of action

Anti-inflammatory properties

The anti-inflammatory properties of flavonoids are primarily mediated through their ability to inhibit key signaling pathways involved in inflammation. These include the nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways. By modulating these pathways, flavonoids can reduce the production of pro-inflammatory cytokines, chemokines, and adhesion molecules, thereby attenuating the inflammatory response.

Antioxidant activity

Oxidative stress plays a critical role in the pathogenesis of IBD. Flavonoids are potent antioxidants that can neutralize reactive oxygen species (ROS) and enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. This reduction in oxidative stress can help to protect the intestinal mucosa from damage and maintain the integrity of the epithelial barrier.

Modulation of gut microbiota

The gut microbiota is increasingly recognized as a key player in the development and progression of IBD. Flavonoids can influence the composition and activity of the gut microbiota, promoting the growth of beneficial bacteria and inhibiting the proliferation of pathogenic species. This modulation of the gut microbiota can enhance mucosal immunity, reduce inflammation, and improve gut barrier function.

Immune regulation

Flavonoids have been shown to modulate both the innate and adaptive immune responses. They can influence the activity of various immune cells, including macrophages, dendritic cells, T cells, and B cells. By promoting a balanced immune response, flavonoids can help to prevent excessive inflammation and tissue damage in IBD.

Effects of flavonoids on intestinal barrier function

The homeostasis in the gastrointestinal tract is functionally maintained by an epithelial barrier, composed by a selective monocellular layer between

the outside lumen and host tissues, which controls the equilibrium between tolerance and immunity to microbes and non-self-antigens. Several defects related to intestinal barrier function have been found in IBD patients. Whether mucosal barrier impairment is a consequence of the inflammatory response or a primary defect that prompts mucosal inflammation is still under debate ^[36]. However, transgenic animal models have clearly demonstrated that a unique defect in the intestinal epithelial barrier is enough to trigger the development of chronic gut inflammation ^[42]. In addition, several studies suggest that the impairment of the epithelial barrier function can be considered as one of the early events that occur in intestinal inflammation, since it facilitates the entry of antigens from the intestinal lumen to the mucosa that may prompt the uncontrolled and exacerbated immune response ^[37, 38]. For this reason, its recovery may contribute to the beneficial effects produced by flavonoids in experimental colitis models. It has been reported that different flavonoids such as quercitrin ^[36], rutin ^[63], hesperidin ^[39] and morin ^[53] improve the colonic absorptive function greatly compromised in experimental colitis, leading to fewer diarrhea symptoms, which are frequent in intestinal inflammation. The flavonoid anti-diarrheal effects have also been related to their capacity to inhibit muscle contractility, enhance intestinal motility and reduce fluid intraluminal accumulation in the gut lumen, as evidenced in different experimental studies ^[40, 41, 42].

Moreover, Azuma *et al.* (2013) ^[59] also reported that naringenin treatment in colitic mice resulted in an improvement in the epithelial barrier permeability, through the preservation of the intestinal tight junction barrier function and structure, which have been described to be compromised after DSS administration ^[43, 44]. *In vitro* studies have confirmed the ability of flavonoids, such as naringenin, daidzenin and morin, to enhance epithelial barrier function. In particular, the incubation of these flavanones with human intestinal Caco-2 epithelial cells resulted in an increased transepithelial electrical resistance (TER) across the cell monolayers, which correlates to an improvement of tight junction integrity ^[45]. This was confirmed by immunoblot analysis and confocal microscopy, which demonstrated that naringenin, daidzenin and morin increase the cytoskeletal expression of the tight junction proteins as well as their assembly, thus reinforcing epithelial integrity in this cell line ^[45]. In addition to a direct effect on tight protein function, indirect mechanisms can also account for the beneficial effects of flavonoids in preserving the intestinal barrier function. In fact, it has been reported that pro-inflammatory cytokines, such as IFN γ , TNF α or IL-6, can disrupt the epithelial barrier function by apoptosis-independent mechanisms ^[43, 46]. In consequence, the inhibitory effect exerted by these compounds on

the expression of IFN γ and IL-6 can also contribute to the improvement of the intestinal permeability observed in DSS experimental colitis ^[47].

Clinical evidence

Preclinical studies

Numerous preclinical studies have demonstrated the potential benefits of flavonoids in animal models of IBD. For instance, quercetin, a flavonol found in onions and apples, has been shown to reduce colonic inflammation and improve histopathological scores in mice with experimentally induced colitis. Similarly, epigallocatechingallate (EGCG), a flavanol found in green tea, has been shown to inhibit NF- κ B activation and reduce the production of pro-inflammatory cytokines in animal models of IBD.

Human studies

While preclinical studies provide promising evidence, clinical studies on the effects of flavonoids in IBD patients are limited and have yielded mixed results. Some clinical trials have reported improvements in disease activity and quality of life in IBD patients following supplementation with specific flavonoids. For example, a randomized controlled trial investigating the effects of curcumin (a polyphenol related to flavonoids) in UC patients found significant reductions in disease activity and relapse rates. However, other studies have failed to demonstrate significant benefits, highlighting the need for further research to determine the optimal types and doses of flavonoids for IBD treatment.

Practical considerations

Dietary sources

Incorporating flavonoid-rich foods into the diet is a practical approach to harness their potential benefits. A diet rich in fruits, vegetables, nuts, seeds, and whole grains can provide a diverse array of flavonoids. Some specific dietary sources include:

- Berries (e.g., blueberries, strawberries, raspberries).
- Citrus fruits (e.g., oranges, lemons, grapefruits).
- Leafy greens (e.g., spinach, kale).
- Tea (green, black, oolong).
- Dark chocolate.
- Red wine (in moderation).

Table 1: Effects of flavonoids rich-foods against lifespan-shortening diseases

Type of flavonoids rich-food	Biological and pharmacological effects
Pomegranate	Anticancer
Fruits/vegetables	Anti-hypertension, reduced risk of diabetes, anti-hypercholesterolemia, anti-obesity, ↓ cardiovascular diseases, ↓ breast cancer, ↓ coronary heart diseases
Whole grains	Reduced risk of diabetes, anticancer
Coffee	Reduced risk of type 2 diabetes
Berries	↓Prostate cancer, reduced risk of type 2 diabetes
Green tea	Reduced risk of type 2 diabetes, ↓ blood glucose, anticancer
Apple	Reduced risk of type 2 diabetes, ↓ breast cancer, ↓ cardiovascular diseases
Black tea	↓ Blood glucose, ↓ total and LDL cholesterol, ↓ myocardial infarction, reduced risk of coronary heart disease
Onion	Antihyperglycemic effects, ↓ breast cancer
Garlic	Anti-platelet aggregation, modification of LDL, antihyperglycemic effects, anticancer
Cruciferous vegetables	Anticancer
Cabbage	Anticancer, ↓ vascular diseases
Broccoli	Anticancer, ↓ prostate cancer
Cauliflower	Anticancer, ↓ prostate cancer
Brussels sprouts	Anticancer
Soy	Reduced risk of breast and prostate cancer
Citrus fruits	Antiproliferative, ↓ vascular diseases
Tomato	↓ Prostate cancer
Turmeric	Anti-hepatocarcinogenesis, anticancer
Ginger	Inhibit platelet aggregation, anticancer, anti-thrombotic
Carrots	Anticancer

Supplementation

For individuals who may have difficulty obtaining sufficient flavonoids through diet *alone*, supplementation may be an option. However, it is important to consider the quality, purity, and bioavailability of flavonoid supplements. Consulting with a healthcare provider before starting any new supplement regimen is advisable, particularly for individuals with IBD, as certain supplements may interact with medications or exacerbate symptoms.

Future directions

The potential role of flavonoids in the management of IBD is an exciting area of research that warrants further exploration. Future studies should focus on:

Flavonoid as anti-cancer agents

Epidemiological studies

Numerous epidemiological studies have been undertaken to establish the protective role of flavonoids in cancer prevention. Some research indicates that higher consumption of lignans and elevated plasma levels of their metabolites correlate with a lower incidence of estrogen-related cancers (Pietinen *et al.* 2001; Dai *et al.* 2002; Boccardo *et al.* 2004; McCann *et al.* 2004) although this is not universally supported across all studies (Kilkinen *et al.* 2004; Zeleniuch-Jacquotte *et al.* 2004) and a prospective study was equivocal (Den Tonkelaar *et al.* 2001). It has been suggested that this inconsistency might have a genetic basis (McCann *et al.* 2002). Increased consumption of isoflavones has also been associated with decreased risk of estrogen-related cancers and vascular diseases (Arai *et al.* 2000; Birt *et al.* 2001). Analysis of four cohort studies and six case-control studies investigating the relationship between flavonoid consumption and cancer risk suggests that flavonoids, particularly quercetin, may lower the risk of lung cancer in two studies, while a third study indicated a non-significant increase in risk. High intakes of quercetin and kaempferol were associated with a 40% and 50% reduction in stomach cancer risk, respectively. However, no significant associations were found between any flavonoids and the risks of bladder or breast cancer (Neuhouser 2004). In a network of multicentric Italian case-control studies including about 10,000 incident, histologically confirmed cases of selected cancers and over 16,000 controls, the association of flavonoids, proanthocyanidins and cancer risk was evaluated by Rossi *et al.* (2010). The findings revealed that total flavonoids, flavanones, and flavonols were inversely associated with oral and laryngeal cancers (ORs of 0.56 and 0.60 for total flavonoids; 0.51 and 0.60 for flavanones; and 0.62 and 0.32 for flavonols, respectively). Furthermore, flavonols were inversely related to laryngeal cancer (OR 0.64), while flavanones showed an inverse relationship with esophageal cancer (OR 0.38). A reduced risk of colorectal cancer was found for high intake of anthocyanidins (OR 0.67), flavonols (OR 0.64), flavones (OR 0.78), and isoflavones (OR 0.76). Inverse relations with breast cancer were found for flavones (OR 0.81) and flavonols (OR 0.80). Flavonols (OR 0.63) and

isoflavones (OR 0.51) were inversely associated to ovarian cancer, whereas flavonols (OR 0.69) and flavones (OR 0.68) were inversely associated to renal cancer. No association between flavonoids and prostate cancer emerged, whereas inverse association was found between proanthocyanidins and colorectal cancer. These associations appeared stronger for proanthocyanidins with a higher degree of polymerization (Rossi *et al.* 2010).

In the European Prospective Investigation into Cancer and Nutrition study (Nothlings *et al.* 2008), the intake of vegetables, legumes, and fruit was significantly associated with reduced risks of CVD mortality and mortality due to non-CVD/non-cancer causes [RR 0.88 (95% CI 0.81-0.95) and 0.90 (0.82-0.99), respectively] in a diabetic population comprising >10,000 individuals. High urinary excretion of both equol and enterolactone (mammalian metabolite of plant lignans) has been found to be associated with a significant decrease in breast cancer risk in an epidemiological case-control study in breast cancer patients (Ingram *et al.* 1997). Although this could suggest the possible importance of isoflavonoid and lignan metabolism in decreased breast cancer risk, the phytoestrogen excretion observed may just be a marker of dietary differences (Barnes 1998). Knekt and co-workers also estimated that men with higher quercetin intake had a lower lung cancer incidence, and men with higher myricetin intakes had a lower prostate cancer risk (Knekt *et al.* 2002).

The intake of flavonoids is not inversely related with bladder cancer or breast cancer risk in some of the studies (Garcia-Closas *et al.* 1999; Peterson *et al.* 2003). Quercetin has been reported to prevent renal cell cancer among male smokers (Wilson *et al.* 2009). A case-control study conducted between 1994 and 2002 in four Italian areas to study the relation between major flavonoid classes and renal cell carcinoma by Bosetti *et al.* 2007 revealed that flavonols and flavones were inversely related to the risk of renal cancer. A cohort of 34,651 postmenopausal cancer-free women revealed inverse relation between catechin intake and rectal cancer (Arts *et al.* 2002).

Population-based case-control studies carried out separately in Hawaii, Uruguay and Spain suggested an inverse association between different cancers (oral cavity, pharynx, larynx and esophagus, lungs, stomach) and total intake of flavonoids, beta-carotene and vitamin E (Le Marchand *et al.* 2000; Stefani *et al.* 1999a, b; Garcia-Closas *et al.* 1999). Inverse association of cholangiocarcinomas (CAC) with flavan-3-ols, anthocyanidins and total flavonoids has been reported and flavones may be inversely associated with hepatocellular carcinoma cells (HCC) risk (Lagiou *et al.* 2008). A

statistically significant association between highest flavonoid intake and reduced risk of developing lung cancer has been reported whereby an increase in flavonoid intake of 20 mg/day was associated with a 10 % decreased risk of developing lung cancer (Tang *et al.* 2009).

Studies examining the relationship between tea, flavonoids, and the risk of lung cancer have suggested a slight positive connection, especially in individuals who have never smoked. Additional carefully planned studies involving large groups of people are necessary to enhance the proof regarding the impact of consuming normal amounts of dietary flavonoids over an extended period. (Arts 2008). Consumption of soy foods rich in isoflavones has been weakly associated with reduced colon and prostate cancer (Adlercreutz2002; Guo *et al.* 2004; Holzbeierlein *et al.* 2005; Goetzlet *et al.* 2007). A protective effect of flavonoids in association with vitamin C has been shown on esophageal cancer using data from case-control study conducted in northern Italy (Rossi *et al.* 2007). Flavonoid-rich diet may decrease pancreatic cancer risk in male smoker's not consuming supplemental alpha-tocopherol and beta-carotene (Bobe2008).

- Conducting large-scale, well-designed clinical trials to establish the efficacy and safety of flavonoid supplementation in IBD patients.
- Investigating the synergistic effects of different flavonoids and other bioactive compounds in combination.
- Exploring the mechanisms underlying the interactions between flavonoids and the gut microbiota.
- Identifying biomarkers to predict individual responses to flavonoid interventions.

Conclusion

Flavonoids represent a promising adjunctive therapy for the management of Inflammatory Bowel Disease. Their anti-inflammatory, antioxidant, and immunomodulatory properties, coupled with their ability to modulate the gut microbiota, make them an attractive option for reducing inflammation and improving gut health. While the current evidence is encouraging, further research is needed to fully elucidate the therapeutic potential of flavonoids in IBD and to develop evidence-based dietary and supplementation guidelines for patients. Integrating flavonoid-rich foods into a balanced diet may offer a natural and holistic approach to support the management of this challenging condition. The mortality of patients with IBD is about 1.5-5 times higher compared to the general population. Patients with Crohn disease suffer the highest morbidity and mortality. The major

cause of death includes infections, the progression of the disease, surgical complications, and multiorgan involvement. More important, patients with IBD also have a high rate of colorectal cancer. Patients who develop pancolitis have the highest risk of colon cancer within two decades. Hence screening colonoscopy is recommended at 1 to 2 year intervals.

In addition to the disease, these patients are also managed with potent medications like steroids and biological agents, which have a host of adverse effects. Thus, the pharmacist should be alert for any adverse reaction. Patients with IBD are also at risk for asthma or COPD.

Finally, IBD has enormous mental morbidity. Many patients develop depression, suicidal tendencies, and anxiety. Thus, at every visit, the nurse should monitor the patient's mental status and make appropriate referrals.

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Chapter - 5

Nanotechnologies in Pharma

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Chapter - 5

Nanotechnologies in Pharma

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Sanjari Rupapara and Priyanka Hagawane

Abstract

Today's growing population has led to a sharp rise in the need for healthcare facilities. There is unquestionably a big need to introduce and develop new technology into the pharmaceutical business, as this demand will only grow. Information about nanotechnology applications in pharmacy is included in this chapter ^[1]. Any material with at least one dimension between one and one hundred nanometres is considered a nanoparticle. Size reduction is the most crucial unit activity in pharmacy. Size reduction results in improved stability, decreased toxicity, enhanced bioavailability, increased rate of release, and favorable drug formulation prospects. These days, the performance of many dosage forms has improved due to improvements in nanoscale size. For instance, a given unit's payload size is nanometre 10-9 meters ^[2]. One recent development in pharmacology is nano pharmacology. Nanoscience and nanotechnology are growing in the realm of nanomedicine. By designing drugs and delivering them to specific targets, nano pharmacology aims to enhance pharmacodynamics and kinetic profiles for safer and more effective treatment.

Keywords: Microneedles, reduced toxicity, enhanced drug formulation, nanoparticles in cancer treatment, and nano-pharmacology

Overview

It was Japanese physicist Norio Taniguchi who initially used the term "nanotechnology". The Greek term "Nanos", which means dwarf or little, is where the name "nanotechnology" originates ^[3]. Different features emerge at the nanoscale, giving nano-objects unique characteristics such as being faster, lighter, more cost-effective, more energy-efficient, and able to fit through microscopic gaps.

Nanotechnology has enormous promise to improve medicine in areas including drug delivery, diagnostic tools, and imaging in medicine, impacting

areas such as imaging techniques, diagnostic tools, drug delivery systems, tissue engineering, implants, and pharmaceutical therapeutics ^[4]. The Surface area rises with decreasing particle size. Increased surface area, better solubility, quicker rates of dissolution, oral bioavailability, and speedier therapeutic action are some of the main advantages of nanosizing.

The dimensions of a structure determine its classification: a single dimension in the nanoscale is called a quantum well; two dimensions in the nanoscale are called a quantum wire; and three dimensions in the nanoscale are called a quantum dot. Depending on the manufacturing process, pharmaceuticals can be made into nanoparticles, nanospheres, or nanocapsules, which enable drugs to be dissolved, encapsulated, trapped, or connected to nanoparticle matrices ^[5]. Precise medication distribution is made possible by nanotechnology, which is vital for personalized treatment and for stimulating therapeutic innovation in the pharmaceutical industry ^[6].

Scope and Opportunity

Nanotechnology is a key component of the pharmaceutical business and has become one of the most important and effective instruments available. It helps identify several illnesses, such as viral and bacterial infections and degenerative disorders. Numerous nano-based systems established in pharmacy, including metallic nanoparticles, carbon nanotubes, dendrimers, nanofibers, and quantum dots, are applied with nanotechnology.

It is anticipated that pharmaceutical nanotechnology, a fast-expanding discipline with cutting-edge and highly specialized methods, will soon completely transform the pharmaceutical sector. It is reasonable to assume that this industry will grow rapidly given its potential, particularly with the advent of medications based on nanotechnology. When compared to conventional techniques, nanotechnology provides. In comparison to traditional methods, nanotechnology offers a superior alternative for drug delivery.

The range of pharmaceutical nanotechnology is vast, and several applications include:

- 1) Tissue engineering
- 2) Nano-medicines
- 3) Nano-robots
- 4) Biosensors
- 5) Biomarkers
- 6) Advanced drug delivery systems

- 7) Image enhancement devices
- 8) Bioactive surfaces
- 9) Implant technology
- 10) Diagnostic tools
- 11) Artificial red blood cells, among others, Potential avenues in nanotechnology.

There is a growing demand for pharmaceutical research in nanotechnology, leading to the development of innovative drug formulations. The interdisciplinary nature of nanotechnology encourages collaboration between pharmacists, chemists, biologists, and material scientists, fostering innovation in drug development and healthcare solutions.

Role of nanotechnology in pharmaceutical field

The creation of pharmaceutical products benefits greatly from nanotechnology since it can improve drug delivery, increase therapeutic efficacy, and lessen negative effects. The following are some important applications of nanotechnology in the pharmaceutical industry:

- 1) **Targeted drug delivery:** By creating nanoparticles specifically designed to transport medications to particular cells or tissues, treatment accuracy can be increased. In diseases like cancer, where targeting tumor cells can lessen damage to good tissue, this is particularly crucial. Doxil®, a liposomal version of the chemotherapeutic medication doxorubicin, is a prime example of pharmaceutical nanotechnology in action. Doxil® employs nanotechnology to boost drug delivery by liposome encapsulation, which prevents immune system detection and increases penetration and retention time.
- 2) **Improved solubility and bioavailability:** There are seen limitations in the effectiveness of many drugs that have poor solubility. Rapamune® is an immunosuppressant used to prevent organ rejection after transplantation. It utilizes nanotechnology to improve the drug's solubility and bioavailability. Sirolimus, the active ingredient, is poorly water-soluble, which limits its absorption in the body. Sirolimus is formulated into nanosized crystals, typically below 200 nm. By reducing the drug particle size to the nanoscale, the surface area exposed to the dissolution medium increases dramatically, improving its solubility fastens dissolution, and gives better bioavailability.

- 3) **Controlled release:** The need for healthcare facilities has sharply increased as a result of the world's population growth. Given that this need will only increase, there is without a doubt a great need to introduce and develop new technology in the pharmaceutical industry. This chapter contains information regarding the applications of nanotechnology in pharmacy.
- 4) **Crossing biological barriers:** A material is regarded as a nanoparticle if its dimensions are at least one hundred nanometers. In pharmacy, size reduction is the most important unit activity. Reducing size improves stability, lowers toxicity, increases bioavailability, speeds up release, and offers favorable opportunities for medication formulation. These days, advancements in nanoscale size have increased the performance of numerous dosage forms. For example, the payload size of a given unit is 10^9 meters, which helps them navigate through the tight junctions of the BBB. The nanoparticles are specifically targeting ligands (such as transferrin or lactoferrin) that have the specialized function of binding to receptors on the BBB and releasing them in a controlled manner in the brain.
- 5) **Reduced toxicity and side effects:** The need for healthcare facilities has sharply increased as a result of the world's population growth. Given that this need will only increase, there is without a doubt a great need to introduce and develop new technology in the pharmaceutical industry. This chapter contains information regarding the applications of nanotechnology in pharmacy. Abraxane® utilizes nanotechnology to develop a solvent-free formulation of paclitaxel. This eliminates the need for toxic solvents like Cremophor EL.
- 6) **Diagnostic tools:** A material is regarded as a nanoparticle if its dimensions are at least of one hundred nanometers. In pharmacy, size reduction is the most important unit activity. Reducing size improves stability, lowers toxicity, increases bioavailability, speeds up release, and offers favorable opportunities for medication formulation. These days, advancements in nanoscale size have increased the performance of numerous dosage forms. For example, the payload size of a given unit is 10^9 meters.
- 7) **Vaccine development:** Nanoparticles can be used to create more stable and effective vaccines by enhancing the immune response or by improving the stability of vaccines that require precise delivery systems, such as mRNA vaccines. An example of nanotechnology

used in vaccine development is the application of lipid nanoparticles (LNPs) in mRNA vaccines, particularly in the development of COVID-19 vaccines. The mRNA, which encodes the spike protein of the SARS-CoV-2 virus, is encapsulated within lipid nanoparticles. These nanoparticles are typically around 80-100 nm in size. And protect the mRNA from degradation by enzymes present in the body. In summary, nanotechnology offers innovative solutions in pharmaceutical product development by enhancing the safety, effectiveness, and delivery of drugs, ultimately leading to more personalized and effective treatments for patients ^[31].

Advantages and benefits of nanotechnology in Pharma field

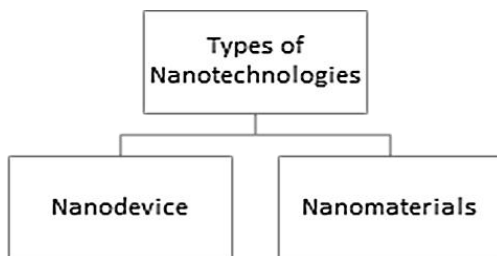
Nanotechnology offers several key advantages in the pharmaceutical field, particularly for drug delivery systems. Here are the main benefits:

- **Targeted drug delivery:** Nanoparticles can deliver drugs directly to specific sites, like tumors, reducing dosage and side effects while improving effectiveness.
- **Improved solubility and stability:** Nanoparticles enhance the solubility and stability of poorly water-soluble drugs, making them more effective.
- **Biodegradability:** Many nanoparticles are biodegradable, allowing for controlled and safe drug release in the body.
- **Enhanced bioavailability:** Nanoparticles improve drug absorption and distribution, increasing effectiveness with lower doses and reducing toxicity ^[7].
- **Controlled release:** Nanotechnology enables the slow, controlled release of drugs, improving treatment outcomes and patient compliance ^[8].
- **Crossing biological barriers:** Nanoparticles can cross barriers like the blood-brain barrier, allowing the treatment of neurological diseases and cancer ^[9].
- **Reduced toxicity:** Targeted drug delivery minimizes exposure to healthy tissues, reducing side effects, especially in chemotherapy ^[10].
- **Personalized medicine:** Nanotechnology supports personalized treatments, tailored to a patient's genetic profile for better outcomes.
- **Improved circulation:** Nanoparticles smaller than 200 nm evade liver and spleen filtration, remaining in circulation longer.

- **Nucleic acid delivery:** Nanotechnology enables the effective delivery of nucleic acids for gene therapies.
- **Multi-drug delivery:** Nanoparticles can deliver multiple drugs simultaneously to tumor sites.
- **Non-drug therapies:** Nanotechnology also supports non-drug treatments like photothermal and photodynamic therapies for cancer.

These benefits highlight the transformative potential of nanotechnology in improving drug delivery and treatment outcomes.

Types of nanotechnologies in pharmacy



Nanodevice are miniature device in nano scale, these include nano and microelectromechanical systems (NEMS/MEMS), microfluidic, and microarrays. For example, biosensors and detectors. They can help in achieving Controlled drug delivery as they can deliver therapeutic and diagnostic agents.

Nanodevices can be used in the formulation of nanomaterials and nanorobots.

Nanomaterials on the other hand are the biomaterials that can be used in dental or orthopaedic implants. They are prepared for enhancing biocompatibility. These materials are further classified into nanocrystalline and nano structured materials. Nanocrystalline can be used as an excipient to replace the one which is less performing. Nanomaterials are used for carrying out functioning of various nanotools like quantum dots, dendrimers, etc. ^[47]

Types on nanosystems

1. Carbon nanotube

Carbon nanotubes are cage like and hollow tubular carbon-based structures. These tubes are made up of cylinders of graphite sheets that are sealed at one or both ends by bucky balls. They can range in length between 1 to 100 nm. Their diameter depends on the number walls in their structure.

They exist in many structures depending upon length, thickness, number of tubes rolled up and type of helicity. They are used for drug encapsulation. They have greater capacity to absorb molecules. Therefore, endocytosis or insertion across the cell membrane is how nanotubes enter the cells. They can be classified into: single walled carbon nanotube (SWCTs) and multi walled carbon nanotube (MWCTs).

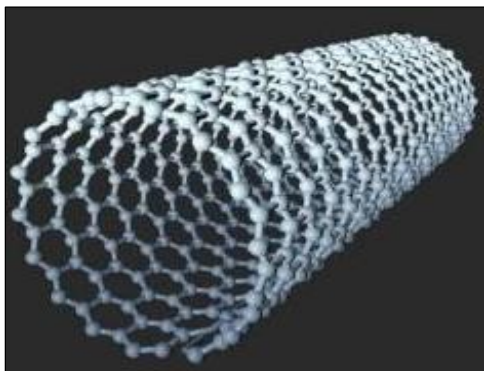


Fig 1: Structure of carbon nanotubes ^[1]

Method of preparation of carbon nanotube Arc discharge evaporation method:

In this method, higher temperatures are used which causes growth of CNTs. In the electric arc method, electric arc is created between two graphite electrode which generates extremely high temperature. At this temperature, carbon is sublimated, its vapours are cooled and condensed and this results in formation of either MWCNTs or SWCNTs. MWCNTs are formed without addition of a catalyst and to produce SWCNTs, catalysts like Fe, Co and Ni are added. Initially this method was used to produce C₆₀ fullerenes ^[32].

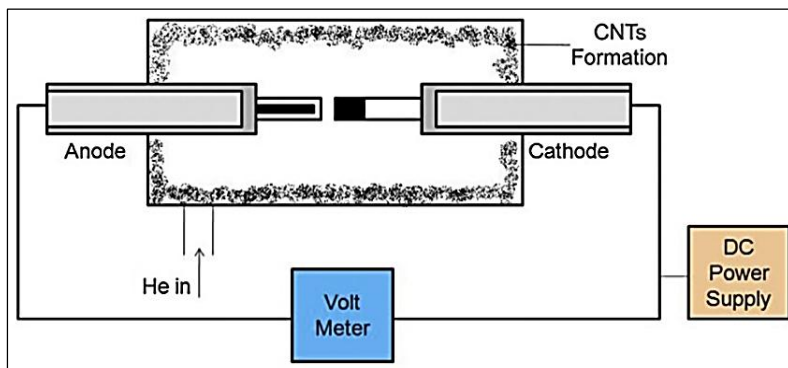


Fig 2: Schematic of arc discharge to produce CNTs. ^[32]

2. Dendrimers

Dendrimers are multi-branched polymers whose size and shape can be controlled. A single dendrimer has an ability to hold many molecules ranging from recognizing molecule to therapeutic agent. As it has a characteristic structure, drugs are filled in it by either covalent conjugation or electrostatic absorption. Its branching can be controlled and by creating a spherical branching, it can be used for drug delivery or entrapment.

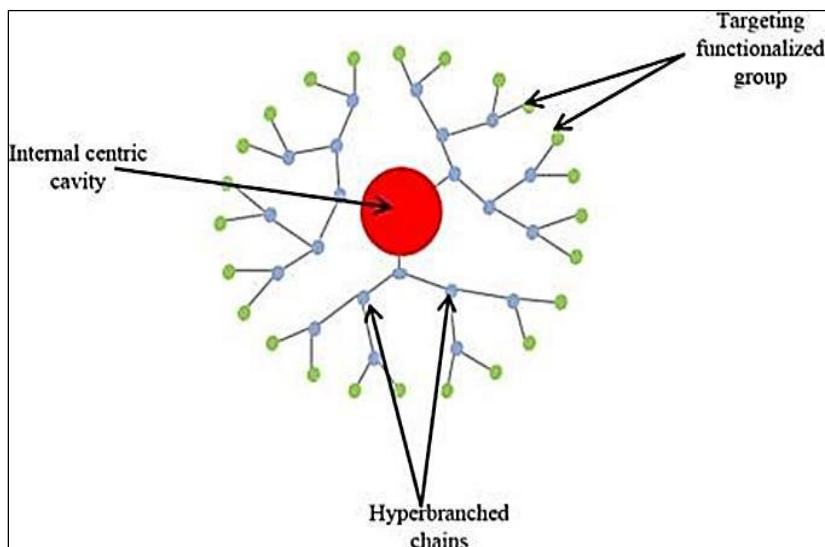


Fig 3: Structure of dendrimer ^[1].

Method of preparation of dendrimers

Divergent method

In this method, the multifunctional core is extended outward radially. This process is carried out by Michael addition reaction. Incompletion of any step in this step can lead to nonuniformity in the length of branches of dendrimer. This may lead to asymmetry and change in functionality. ^[33]

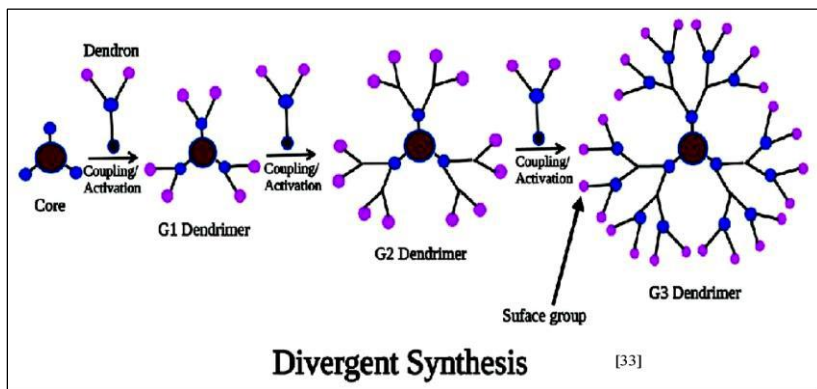


Fig 4: Divergent synthesis of dendrimers.

3. Ceramic nanoparticles

Ceramic nanoparticles are the particles made from silica, titania, alumina, etc. and these elements are compatible with biological system. Different functional group may also be added to modify its surface. They protect the drug from the external pH and temperature which may cause its denaturation. They can be used for drug entrapment and target drug delivery *in vivo*.



Fig 5: Ceramic nanoparticles ^[1]

Method of preparation of ceramic nanoparticles

Pulse laser ablation

In this method, the sample is placed in a vacuum chamber. On the sample, a high-pulsed laser beam is focused and the plasma is generated, which is then transforms the sample into a colloidal solution of nanoparticles. To formulate the nanoparticles, second-harmonic group type laser is constantly used ^[34].

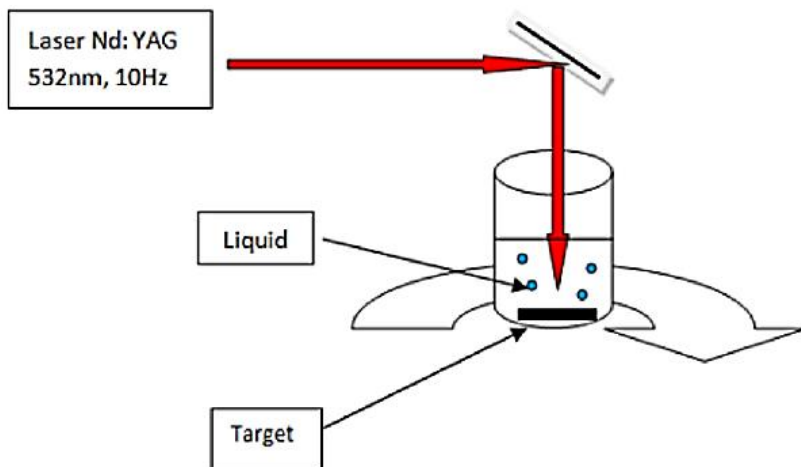


Fig 6: Preparation of nanoparticles by laser in solution ^[34]

4. Fullerenes

These are allotropes of carbon. Its carbon atom is connected with single and double bonds. Fullerene exists in various size and shapes including hollow sphere, ellipsoid and tube shape. The spherical fullerene is known as buckyballs and can be considered as graphite layers. Buckyballs can be used as an alternative to CNTs and graphene. C60 fullerene which is a buckyball is most used in comparison to CNT or graphene because it poses zero-dimensional geometry. It can be used as lubricant in industrial application.

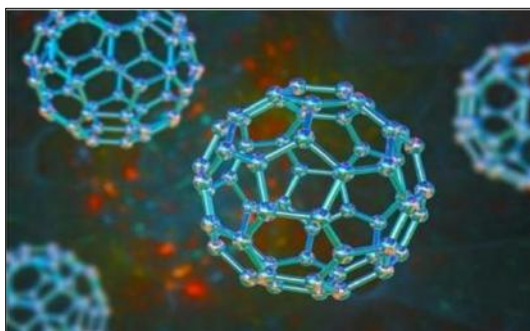


Fig 7: Structure of fullerenes ^[1]

Method of preparation of fullerenes

Synthesis of fullerene-rhodium nanocomposite powders by aerosol decomposition method: In this method, two solutions of precursor are prepared: first contains mixed fullerene extract in toluene and second contains

mixed fullerene extract and [(1,5-COD) RhCl]₂ rhodium-based compound in toluene. In the first step, the precursor is evaporated, followed by precipitation and decomposition under specific environmental condition. Finally, the powder is collected ^[35].

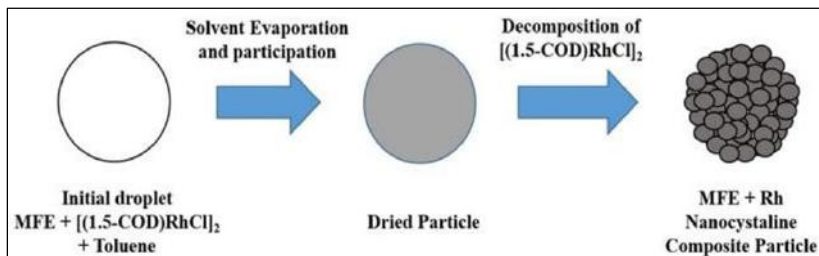


Fig 8: Schematic of generation of fullerene-rhodium nanocomposite powders via aerosol decomposition ^[35]

5. Metallic nanoparticle

Nanoparticles can be formed using various metals even silver and gold. Silver and gold nanoparticles are important for biomedical use. They can be used as an alternative to quantum dots.

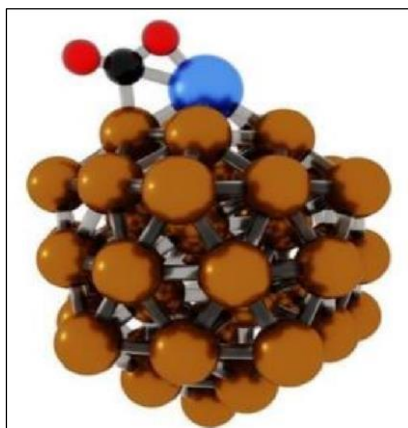


Fig 9: Structure of metallic nanoparticle ^[1].

Method of preparation of metallic nanoparticle

Production of pre-formed nanoparticles in the gas phase

All techniques utilized for generating gas-phase nanoparticles include the creation of super-saturated metal vapors that subsequently condense into particles. These condensed particles are filtered by mass and either collected in an ion trap or deposited on a surface, or they can be co-deposited with atomic vapor from another material to form matrix-isolated nanoparticles ^[36].

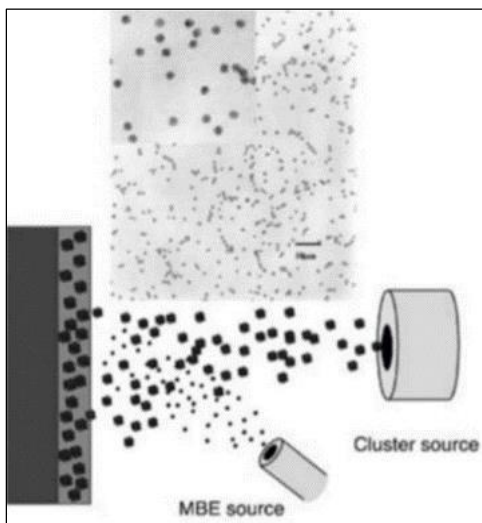


Fig 10: Production of gas-phase particles ^[36]

6. Magnetic nanoparticles (MNPs)

They are colloidal suspension of magnetic particles in liquid carrier. They are also known as magnetic beads (MB) or micro-and nano-sized magnetic beads or ferrofluids or magnetic fluids. They can be used in targeted drug delivery and also can be used to produce new material and devices.

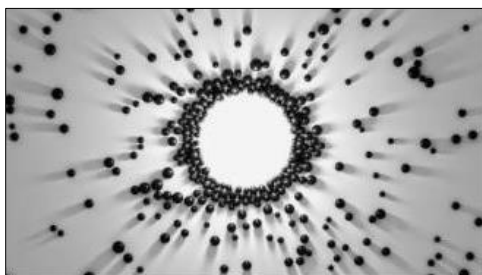


Fig 11: Structure of metallic nanoparticle ^[1]

Methods of preparation

Micro-emulsion technique

In this approach, the solution is typically composed of three phases:

1. A polar phase (water).
2. A nonpolar phase (oil).
3. A surfactant.

These emulsions remain stable due to the surfactant molecules. The surface layer forms various microstructures, resembling a “sponge” phase, where water droplets are dispersed in a continuous oil phase (W/O-reverse micelle) and oil droplets are dispersed in a continuous water phase (O/W-normal micelle). These nano-droplets serve as nano-reactors. Through their ongoing interactions, they tend to merge and break apart, mixing the inorganic salt and precipitating agent to generate a precipitate following nucleation and growth. Lastly, the surfactant is eliminated and rinsed twice to yield nanoparticles ^[37].

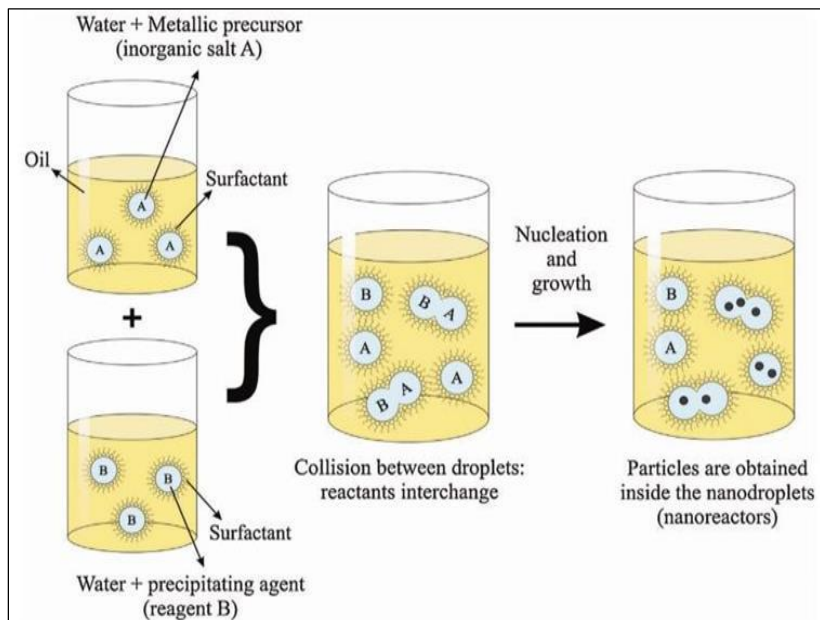


Fig 12: Scheme of an oil-in-water (O/W) micro-emulsion reaction method for synthesis of nanoparticles ^[37]

7. Nanocomposite

Nanocomposite is made up of two or more different material and among these, any one material is in nano range. Nanosized particles in nanocomposite have high surface area. It consists of one or more discontinuous phase dispersed through continuous phase. The continuous phase is known as matrix while discontinuous phase is known as reinforcing material.



Fig 13: Structure of nanocomposite ^[1]

Method of preparation

Cold spray method

This method fabricates coating below the melting point of the material. This method avoids deterioration of the material. Coatings obtained have low porosity (280 MPa) and strong adhesion (>70 MPa). This method produces nanocomposite coating having metallic matrix (such as Cu, Al, Co) or alloy matrix ^[38].

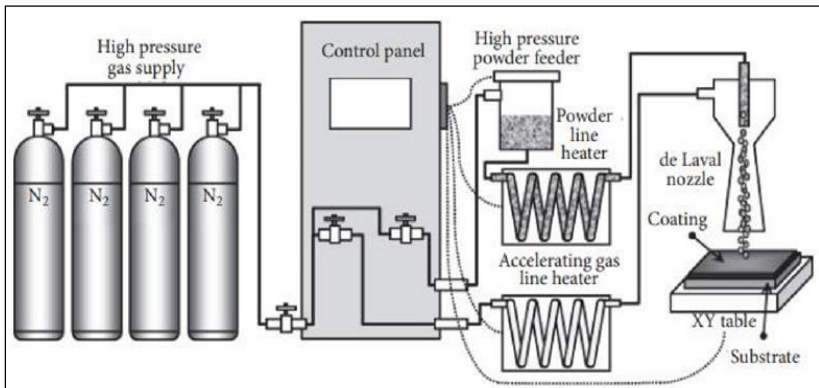


Fig 14: Principle of cold spray technique for preparation of nanocomposite ^[38]

8. Nanopores

These are the nano meter scale holes. They are formed by proteins or cells naturally and allows passage for ions between nerve cells. Similar nanopores are produced artificially because they provide thermal insulation, controllable material separation and release. One of the examples of nanopores material is aerogel produced by sol-gel method.

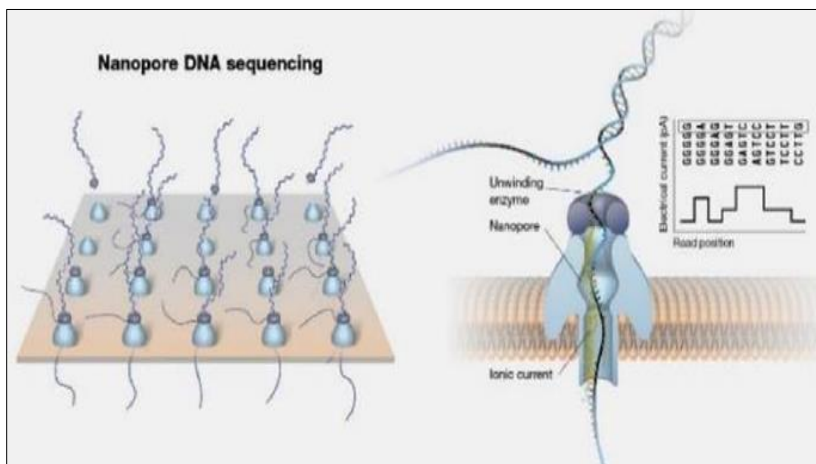


Fig 15: Structure of nanopores ^[1]

Method of preparation

The membrane undergoes a treatment with -wave UV radiation for an entire night. Asymmetric chemical etching produces conically shaped nanopores. The membrane is then positioned in a conductivity cell, with one side oriented towards the UV-treated surface filled with an alkaline etching solution (9 M NaOH), while the opposite half-cell contains the stopping solution (1 M HCOOH and 1 M KCl). Platinum electrodes are submerged in both cells, and a transmembrane potential of 1 V.

9. Nano shells

Nano shells have a dielectric core of silica and outer layer consist of metal. The ratio of core and shell can be changed and this affects its characteristics. Hence, they can be used to create new system with different morphologies. In nano shells precious materials can be used to coat an inexpensive core for example gold nano shell which is used for cancer detection.

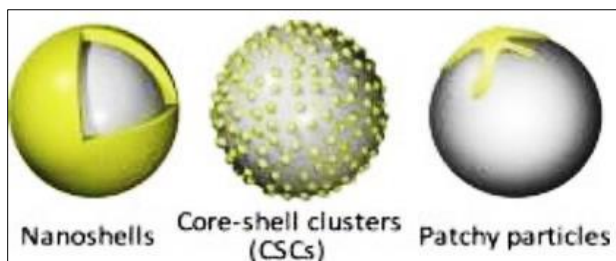


Fig 16: Structure of Nano shells ^[1]

Method of preparation

Synthesis of 2.3 ± 0.5 nm Gold Nanoparticles

In a beaker, 3.425 g of PVP-55000 was dissolved in 190 ml of water under a magnetic stirrer for 15 min. to this solution, 4.075 ml of 20 mM HauCl_4 solution is added followed by rapid addition of 57 ml of 5.27 mM NaBH_4 solution to the vortex of PVP- HauCl_4 mixture with vigorous stirring. Formation of gold particles is indicated by the conversion of light-yellow colour to dark brown colour. Stirring is continued for 15 min and the suspension is stored in a dark room. ^[40]

10. Nanowires

These are the one-dimensional semi-conductive and conductive particles containing few dozens of nm crystalline structure with a high ratio of length / diameter. They have characteristic mechanical, electrical, thermal and optical properties. They can be produced by top-down or bottom-up method.

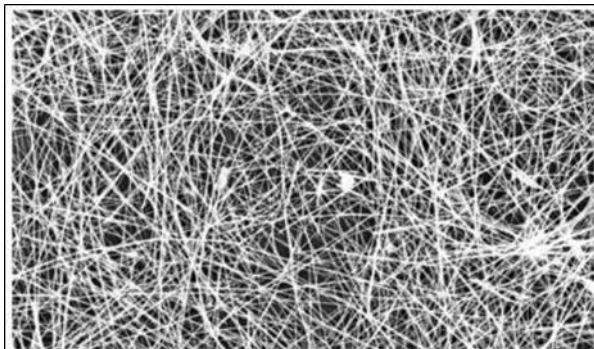


Fig 17: Structure of Nanowires ^[1]

Method of preparation

Solvothermal synthesis

This method is most commonly used to produce crystalline nanowires of semi-conductor materials. In this method, a solvent is metal precursors and crystal growth regulating or templating agents, such as amines. The autoclave is maintained at relatively high temperature and pressure and the prepared solution mixture is placed into it to promote growth of crystals ^[41].

11. Polymeric micelles

These are nanoscopic core/shell structures consisting of a lipophilic and a lipophobic monomer units in a block copolymer. Its centre is lipophilic. This system improves solubility of a weakly watersoluble drug. This improves

permeability of the drug across physiological barriers and improves bioavailability. This system can be used for targeted drug delivery.

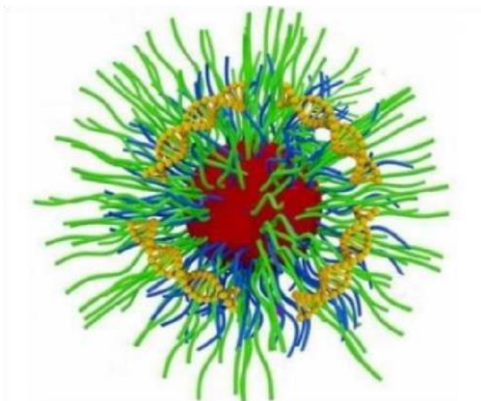


Fig 18: Structure of Polymeric Micelles ^[1]

Method of preparation

Dialysis

In this method, PEG-DSPE film is formed in RBF by evaporating chloroform. Vacuum is applied if necessary. By vortexing, samples were mixed for 15-20 min and incubated in the shaker overnight. The concentration of CPT was estimated by measuring its fluorescence. In rotary evaporator, organic solvents were removed under vacuum and drug-polymer film was obtained. The film is extremely vortexed to form micelles ^[42].

12. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are primarily known for being biodegradable and biocompatible. They can be categorized into two types: vesicular systems (nano capsules) and matrix systems (nanospheres). These nanoparticles can contain active substances either trapped within or adhered to the outer layer of a polymeric core. PNPs have the potential to serve as systems for intracellular and targeted delivery, making them useful for transporting encapsulated medications.

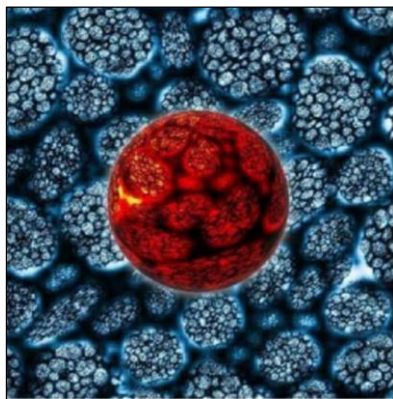


Fig 19: Structure of Polymeric Nanoparticle ^[1]

Method of preparation

Chemical reaction-induced self-assembly

Heat is provided to diblock, poly (4-methyl styrene-block-phenyl vinyl sulfoxide) (PMS-b-PVSO), in THF, the soluble and flexible PVSO block is converted into insoluble and rigid polyacetylene (PA) block by a chemical reaction. This results in the formation of a core-shell nanostructure consisting PA block as a core and PMS block as a shell. Rate of the reaction can be controlled by controlling the temperature between 30-80 °C. As the reaction proceeds, colour of the solution changes from colourless to light yellow and finally to dark red ^[43].

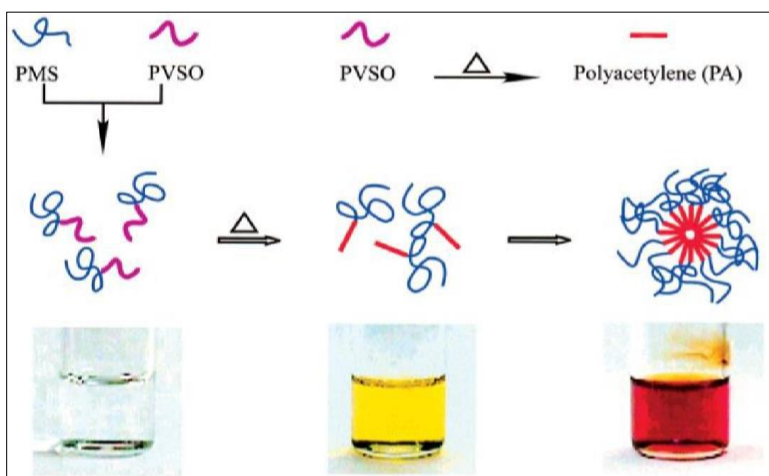


Fig 20: Chemical Reaction-Induced Self-Assembly for formation of polymeric nanoparticle ^[43]

13. Polyplexes

Polyplexes (PPs) are complexes formed spontaneously through the electrostatic attraction between nucleic acids and cationic polymers. These structures can occur naturally between nucleic acids and cationic liposomes or polycations (including polycations linked to targeting ligands or hydrophilic polymers). They are utilized in transfection methods and function by safeguarding nucleic acids from degradation by enzymes.

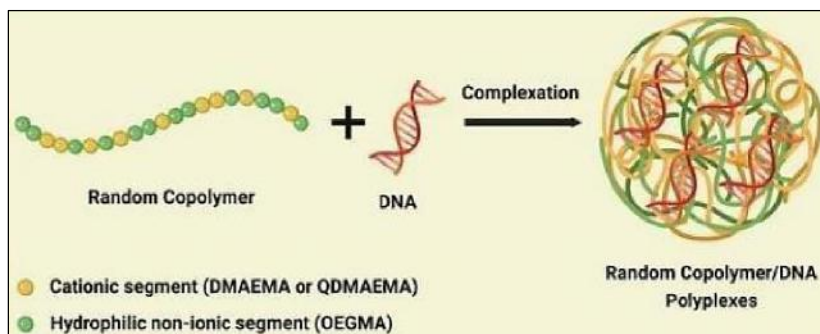


Fig 21: Structure of polyplexes ^[1]

Method of preparation

Formation of polyplexes is usually controlled kinetically. It is performed when the polycation/polyanion association is rapid and irreversible. Further either DNA solution is added to the polymer or vice versa. The sequence of addition influences the polyplexes size and transfection efficiency. Plasmid DNA or RNA is condensed at a specific N/P ratio. Low branched PEI requires higher N/P ratios for a complete condensation of DNA compared to highly branched derivatives ^[44].

14. Quantum dots

Quantum dots (QDs) are nanoscale crystals composed of semiconducting materials, featuring an inorganic semiconductor core (CdSe) that is enveloped by a shell (such as ZnS) to enhance their optical characteristics. They are engineered to emit light when stimulated. There is a cap included that enhances their solubility in aqueous buffers. Their size typically ranges from 2 to 10 nanometers. They have a variety of applications, including cell labeling, biomolecule detection, and serving as non-viral vectors for gene therapy, among others.

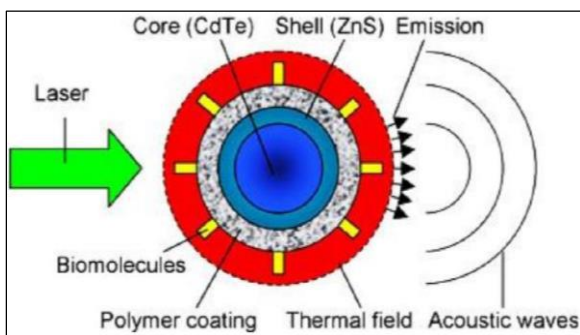


Fig 22: Structure of quantum dots ^[45]

Method of preparation

Hydrothermal synthesis

In this method, the process carried out is crystallization of inorganic salts from aqueous solution which is controlled by pressure and temperature. The solubility of inorganic compounds is directly proportional to temperature and pressure. Therefore, when temperature and/or pressure is lowered, this leads to the formation of crystalline precipitates. Different shapes and sizes of the quantum dots can be achieved by changing pressure, temperature, reaction and aging time and reactants. Passing H₂S gas through precursors has also been used to prepare sulfide-based quantum dots ^[45].

15. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are primarily made up of fatty acids or mono-, di-, or triglycerides. At normal body temperature, they remain in a solid form. Due to their high lipophilicity, they promote transport across the blood-brain barrier (BBB). These colloidal carriers, ranging from 50 to 1,000 nm, consist of physiological lipids dispersed in water or an aqueous surfactant. Their development arose from the substitution of liquid lipids with solid lipids, leading to the formation of solid lipid nanoparticles

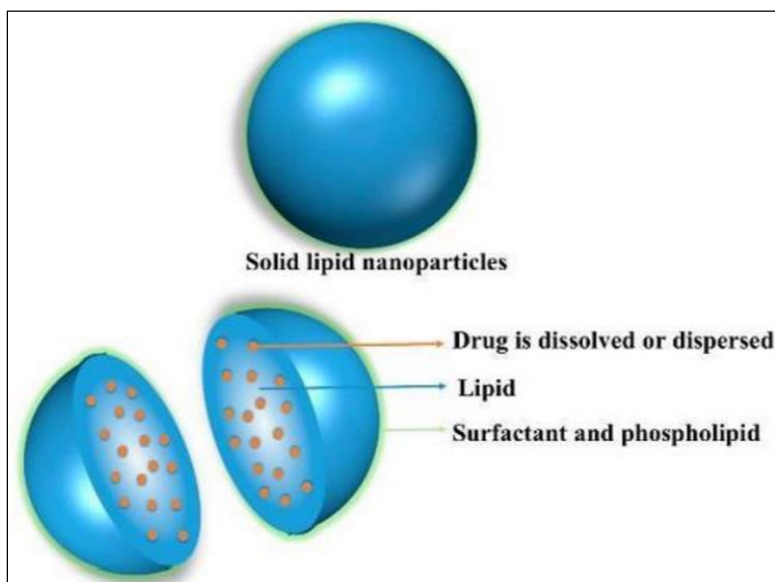


Fig 23: Solid lipid nanoparticles ^[1]

Method of preparation

Spray drying method

In this method, solutions and suspensions are converted into solid dry powder which enhance its stability. It is a one-step procedure, in which liquid feed is converted into a dried atomized state. Initially the feed is converted into spray form via different atomization methods, which then is instantly put in contact with thermal hot gas, this leads to rapid solvent evaporation. Now a cyclone separator and an electrostatic precipitator, separates hot air from dried solid particles ^[46].

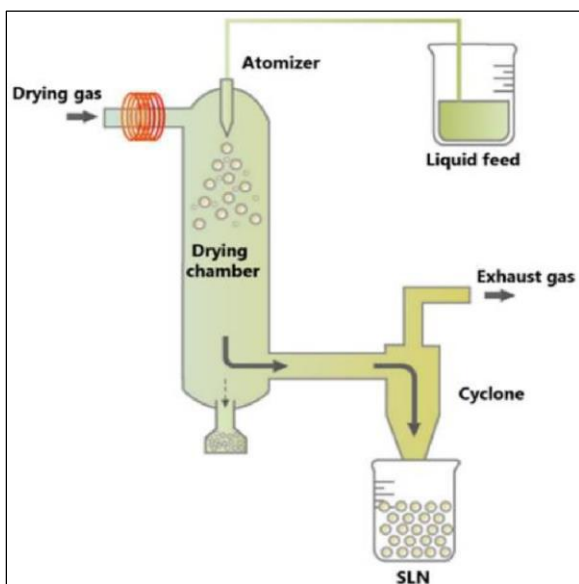


Fig 24: Spray drying method ^[46]

Evaluation parameters

The evaluation of nanoformulations involves a multifaceted approach that considers various parameters to assess their safety, efficacy, and performance. Key evaluation parameters include toxicological metrics, physical characterization and analytical considerations.

Physical characterization

- **Size and surface properties:** Nanoparticle size, shape, and surface charge significantly influence their biological interactions and toxicity ^[48].
- **Rheological and Textural analysis:** For formulations like nanolipid gels, properties such as particle size, polydispersity index and zeta potential are vital for evaluating performance in applications ^[49].

Analytical considerations

- **Quality control:** A systematic approach to manufacturing and analytical evaluation is necessary to ensure the quality and safety of nano-drug products ^[50].

Toxicological metrics

- **Dose metrics:** Traditional mass-based dosing is inadequate for nanomaterials; alternative metrics like particle number, volume and surface area are essential for accurate toxicity assessments ^[51].

- **Toxicity factors:** The number of nanoparticles and their specific toxicity factors are critical in determining their impact on biological systems ^[52].

While these parameters provide a comprehensive framework for evaluating nanoformulations, the field is still evolving, and ongoing research is needed to establish standardized guidelines for safety and efficacy assessments.

The evaluation of nanoformulations encompasses various parameters that are critical for assessing their efficacy and safety. Recent studies highlight several key aspects that should be considered when evaluating these formulations.

Dose metrics

- Traditional mass metrics are insufficient for nanomaterials; alternative metrics such as particle number, volume, and surface area are recommended for toxicity studies ^[51].
- A systematic approach is necessary to determine the most appropriate dose metrics for different nanomaterials, as their toxicological profiles can vary significantly based on physical properties ^[51].

Characterization techniques

- Instrumental analysis methods, including size distribution, surface charge and stability assessments, are essential for characterizing nanocapsules ^[53].
- Techniques such as rheological and textural analysis, alongside sensory evaluations, are employed to assess the performance of nanolipid gel formulations ^[49].

Safety evaluation

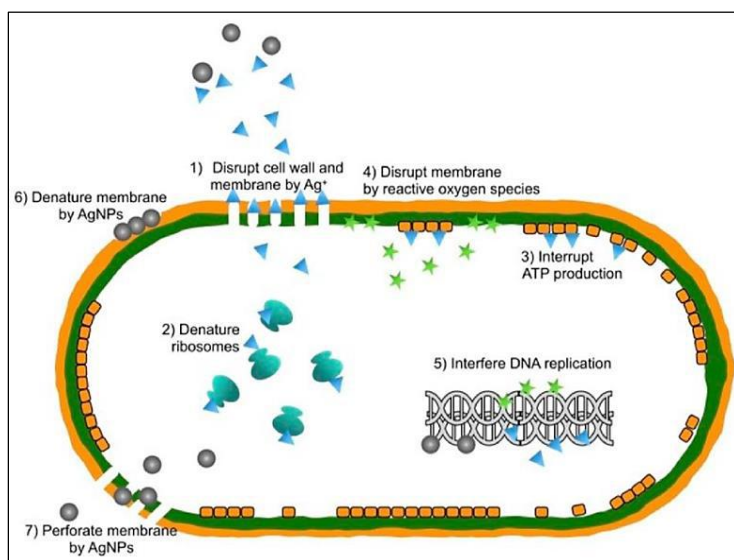
- The safety of nanoparticle formulations is evaluated through in vitro models, focusing on their potential toxicological effects, which can vary based on size, shape, and surface properties ^[48].
- There is a pressing need for novel methods to assess the safety of nanoparticles, particularly in light of regulatory challenges and the complexity of biological interactions ^[48].

While these parameters provide a comprehensive framework for evaluating nanoformulations, ongoing research is essential to refine these methods and establish standardized guidelines for their application in various fields, including medicine and cosmetics.

Application of nano-systems in various diseases

As this field is very diverse, it finds its application in a vast number of diseases. Following is the list of applications of nano-systems in various diseases:

- 1) **Antibacterial treatment:** Antibacterial therapies could involve the use of quantum dots, silver and gold nanoparticles, infrared radiation, and better equipment cleaning ^[12]. One theory about how to kill microorganisms is that silver nanoparticles can continuously discharge silver ions. Silver ions have an affinity for sulfur proteins and electrostatic attraction, which allows them to stick to the cytoplasmic membrane and cell wall. They can pass through bacterial cell walls, altering the composition of cell membranes and perhaps causing cell death. Their enormous surface area-to-volume ratio and nanoscale size both contribute to their efficacy. They can release silver ions, which can disrupt the replication of deoxyribonucleic acid and enhance the permeability of cell membranes. They can also produce reactive oxygen species. The following materials can be treated with silver nanoparticles: adhesive materials in orthodontic treatment; membrane for guided tissue regeneration in periodontal treatment; composite resin in restorative treatment; irrigating solution and obturation material in endodontic treatment; removable denture fabrication in prosthetic treatment; and titanium coating in dental implant treatment ^[13].

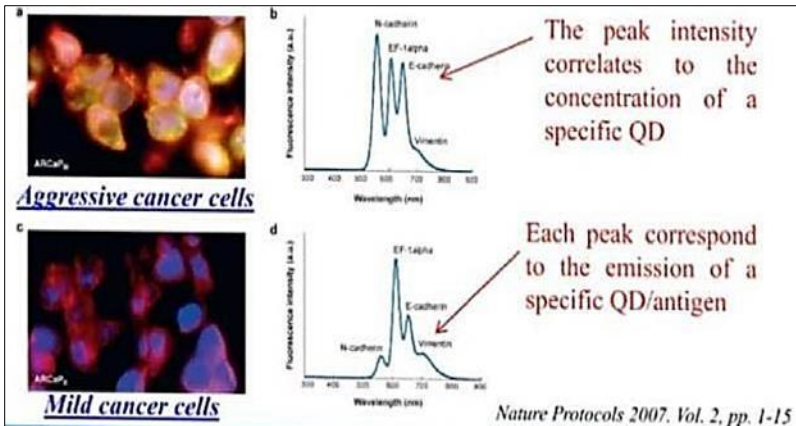


- 2) **Tissue engineering and cell treatment:** The "scaffolding" necessary to build new functional structures that resemble natural tissues and into which live cells can be injected and allowed to proliferate is made possible by nanotechnology. The nanoparticles and cells' biocompatibility with the sample source is advantageous to the emerging tissues. Doctors can then control the processes of cell formation, development, and repair in the resulting tissue ^[12].
- 3) **Wound treatment:** Polymer nanoparticles, nanogenerators, and targeted treatments could improve and expedite the healing of wounds in humans. Only target ligands and images can bind nanoparticles to cells or tissue. This enhances the ability of physicians and radiologists to differentiate between unhealthy and healthy tissue, enhances the management of illnesses, and lowers the risk of damaging healthy tissue. The speed and specificity of biomarker analyses in biological fluids have been significantly impacted by nanotechnology ^[14].
- 4) **In diabetes:** To deliver insulin orally, nanoparticles must pass through epithelial and mucous barriers. The negatively charged mucus layer interacts with cationic nanoparticles, preventing their absorption ^[15]. Although neutral and hydrophilic surface nanoparticles are preferred for removing mucus, their contact with epithelial cells may be hampered ^[16]. Medication loading into nanoparticles can increase the former's stability, shielding it from enzymatic and/or chemical breakdown in the gastrointestinal tract. Moreover, nanoparticles improve the drug's absorption, bioavailability, and residence time by increasing interaction with the GI epithelium. Drugs must be released close to the absorption site since they can become caught in the nanoparticle matrix or adhered to their surface ^[20]. An ideal nanoparticle should enter through the GI membrane, and for that, the nature of the selected polymer, the mean particle size and polydispersity, the surface electrical charge, hydrophilicity, and morphology of the particles are crucial for the nanoparticles uptake in the GIT. One way around the first-pass metabolism of medicines is by lymphatic absorption.

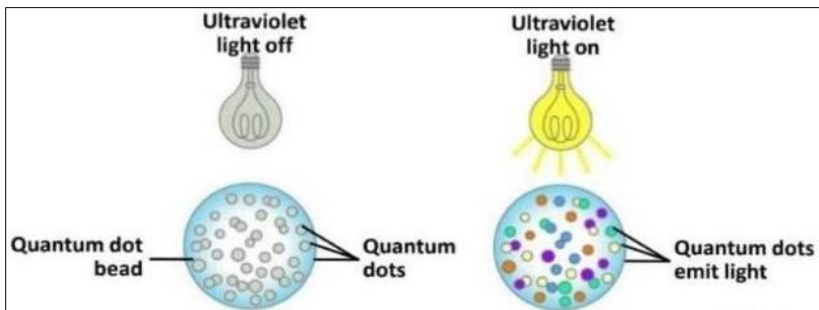
Despite having a network of channels throughout the body, the lymphatic system is thought to be an effective mechanism to transfer oral medications over the intestinal wall since it is a one-way pathway ^[21].

- 5) **Gene therapy:** Gene therapy is a viable treatment option for a number of hereditary illnesses, including hemophilia, cystic fibrosis, and cancers. Gene delivery to the intended location remains an enormous undertaking. Certain genetic materials are naturally unstable. The biological environment quickly destroys them, and genetic material is unable to pass through different cellular membranes. Viral vectors are utilized for the traditional delivery of genes. However, a significant issue with viral vectors is that they could trigger an immune reaction. Non-viral vectors like liposomes, nanoparticles, nanocarriers, etc., can be used to solve this issue. Within the carriers, genetic material may be contained. Plasmid DNA may be efficiently delivered using PLA and PLGA nanoparticles. Gene therapy makes use of chitosan, gelatin, poly-L-lysine, and silica nanoparticles ^[22].
- 6) **Brain targeting:** The brain Barrier (BBB) plays an important role in the targeting of drugs to the entry of potentially toxic chemicals into the brain, but this also prevents entry of desired drug molecules into the brain. By using nanotechnology this hurdle can be removed, as nano-pharmaceuticals can penetrate the brain along with drugs. In vitro studies showed that the use of various nanoparticles enhanced drug delivery to the brain, with reduced oxidative stress, inflammation, and plaque load through the improved delivery of curcumin for treating Alzheimer's disease ^[23]. The applications of liposomes mostly for the treatment of Alzheimer's disease. Poly (ethylene glycol) conjugated polyamidoamine dendrimers have also been used as vehicles for the delivery of drugs and for reducing blood clotting for ischemic stroke therapy ^[25].
- 7) **Ocular diseases:** There are numerous novel ophthalmic drug delivery systems currently being researched, including hydrogels, microparticles, nanoparticles, liposomes, collagen shields, ocular inserts/discs, dendrimers, and trans-corneal iontophoresis. Polymeric nanoparticles can effectively target conditions in the posterior segment of the eye, such as age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis, and retinitis pigmentosa. Ocular drug delivery systems enable both local and systemic drug administration. The nanosuspension technique presents new opportunities for compounds that exhibit poor bioavailability and instability when delivering hydrophobic drugs, especially those with low solubility in both aqueous and organic media.

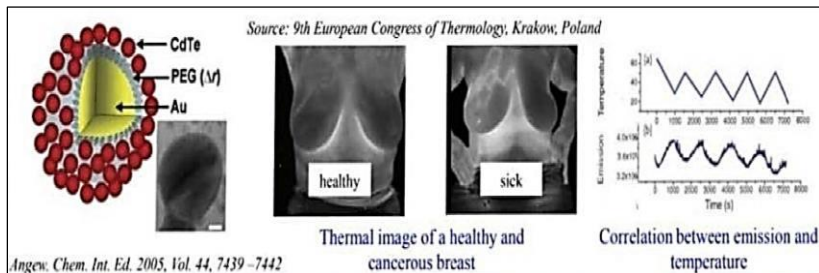
- 8) **Respiratory diseases:** Nanoparticles can be inhaled, penetrating the respiratory tract and settling in the alveoli, where they can engage with epithelial cells and pulmonary surfactant. High-temperature-based targeted drug delivery, utilizing gold nanoparticles (AuNPs) as inorganic nanocarriers, is commonly employed in treating respiratory illnesses.
- 9) **Artificial organs and implants:** Nanotechnology holds potential for the creation of artificial cells, tissues and organs, offering replacements for malfunctioning cells and organs related to metabolic functions that are currently being researched [26].
- 10) **Against cancer:** Nanoparticles have the potential to transport conventional cancer treatments directly to tumors with reduced side effects, facilitating targeted destruction of cancer cells through innovative therapies. Nanodevices can expedite and enhance the efficacy of cancer diagnostics.



Some of the devices are quantum dots, carbon dots, nanothermometers, CT, MRI, etc.

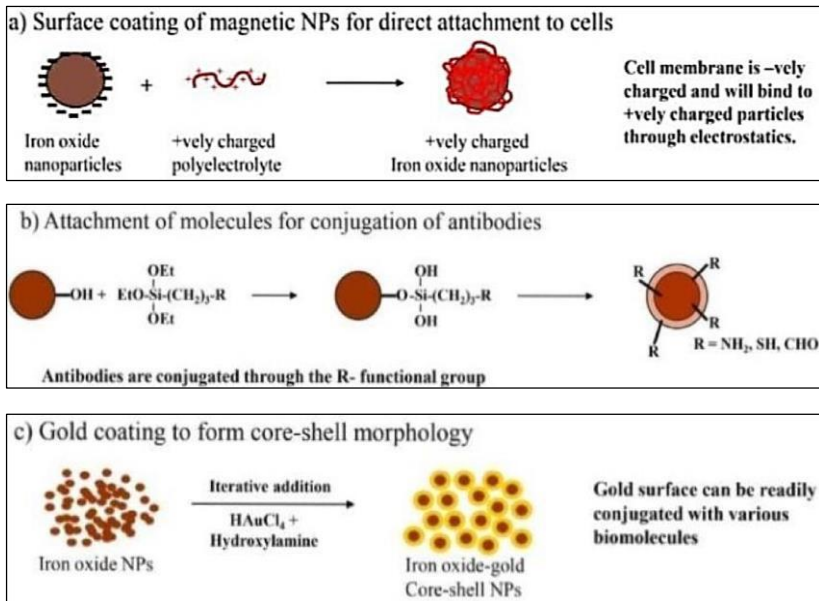


Carbon dots	Quantum dots
Heavy metal core (CdSe, CdTe) associated with toxicity.	Most carbon sources are non-toxic. Inherently bio-compatible.
Intricate synthesis.	Simple synthesis.
Difficult surface functionalization.	Readily surface functionalization.
Poor aqueous solubility.	Highly water soluble.



Nanothermometers

Nanoparticle-mediated cancer imaging: While minimizing macrophage uptake is crucial for nanoparticle-mediated effects in several scenarios, the ability of nanoparticles to undergo macrophage-mediated phagocytosis can be advantageous for imaging purposes^[17]. Titanium dioxide nanoparticles (TiO₂ NPs) might improve CT image contrast and also serve as sensitizers in photodynamic therapy^[18].



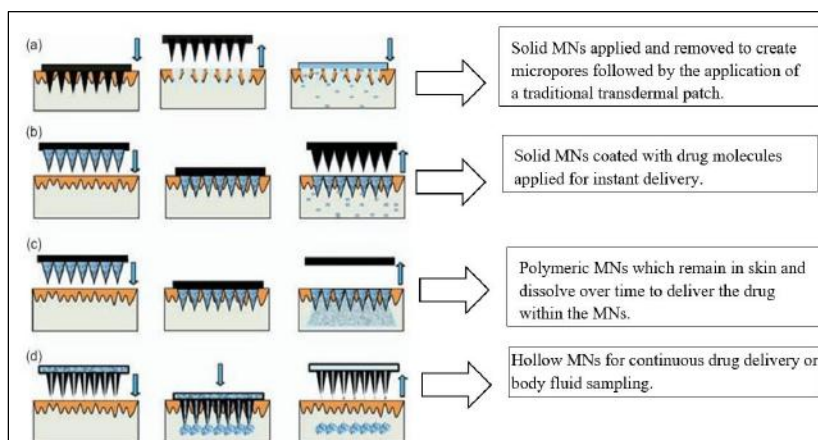
A key fundamental benefit of nanotechnology in cancer therapy is its capability for tumor targeting. Two essential mechanisms differentiate malignant cells from non-malignant ones:

- a) Passive targeting through enhanced permeability and retention (EPR) leverages the physiological properties to raise nanoparticle concentration within tumors.
- b) Active targeting involves specific molecular recognition of antigens, typically proteins found on cancer cell surfaces, to direct nanoparticles to malignant cells, or exploit biochemical traits linked to malignancy, such as the secretion of matrix metalloproteinases.

Passive and active targeting may be deployed independently, or the two approaches may be combined. Both approaches gain from surface modifications of nanoparticles that reduce their uptake by macrophage phagocytosis, thereby maximizing their circulation time ^[19].

Microneedles

Microneedles (MNs) have demonstrated their ability to penetrate skin, effectively moving through the stratum corneum and into the viable epidermis (VE), while avoiding nerve fibers and blood vessels primarily located in the dermal layer. Metal and glass microneedles are efficient at penetrating the skin and can be manufactured at a significantly lower cost compared to silicon microneedles. There are four main methods for transdermal drug delivery facilitated by microneedles ^[27].



Adapted from Arora *et al.*

Human skin is an appealing pathway for drug administration due to its accessibility, which helps bypass firstpass hepatic metabolism. The key

penetration routes through the stratum corneum (SC) barrier include transappendageal, intercellular, and intracellular routes. The trans-appendageal route refers to transport through pores, involving sweat glands and hair follicles along with their sebaceous glands; however, traditional views suggest that this route is not a significant pathway for transdermal delivery since hair follicles and sweat glands comprise only 0.1% of the skin's surface area ^[28]. The intercellular route is the primary entry point for lipophilic drugs because of the tightly packed proteins in corneocytes, rendering them nearly impermeable ^[29]. In the intracellular route, the drug's permeation is mainly influenced by its partition coefficient. Hydrophilic drugs can diffuse through the intracellular route, while lipophilic drugs are more likely to pass through the intercellular pathway ^[30].

Applications of microneedles

Study	Outcome	Reference
Microneedles were created for minimally invasive and painless blood collection.	Blood volumes of up to 840 µL can be extracted to gather biochemical data.	Dae <i>et al.</i> (2018)
Microneedle array electrodes are used in sensors for continuous glucose monitoring.	Microneedles reduce interference when measuring glucose levels, unlike other glucose monitoring devices.	Sanjiv <i>et al.</i> (2017)
Silicon microneedles designed for deep brain drug delivery.	A microarray fabricated on silicon is used for drug infusion in the brain to explore connections and neuronal activities.	Lee <i>et al.</i> (2015)
Targeted administration of antiglaucoma medications to the supraciliary area was achieved using microneedles.	Hollow microneedles were filled with drugs intended for glaucoma therapy and inserted into the eye (intra-ciliary space) as a novel approach.	Kim <i>et al.</i> (2014)
Microneedle biosensors enable immediate electrical detection for on-site cancer diagnosis.	The microneedle sensor integrates high-resolution imaging with realtime electrical detection of cancer, offering a novel approach for cancer identification.	Keum <i>et al.</i> (2015)

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