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THERAPEUTIC ACTIVITIES OF CINNAMIC ACID AND ITS VARIOUS DRUG DELIVERY STRATEGIES: AN INSIGHT

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ABSTRACT

Background: Cinnamic acid is an organic compound with the molecular formula $C_9H_8O_2$. It is a white, crystalline compound that dissolves readily in a variety of organic solvents but sparingly soluble in water. It is a naturally occurring unsaturated carboxylic acid. Cinnamic acid is obtained from cinnamon bark. Cinnamic acid has been utilized as an ingredient in flavours and fragrances. They can regulate the development of the microbes that live on our skin and some of them prevent the production of melanin. The biological efficacy of the synthesized cinnamic acid-derivatives has been found to be significantly influenced by the type of substituents added to cinnamic acid. **Objective:** This review provides an insight into the therapeutic activities of cinnamic acid and its various drug delivery strategies. It also includes different extraction methods along with its comparative studies and its future prospects.

KEYWORDS: Cinnamic Acid, Therapeutic Activity, Drug Delivery.

1. INTRODUCTION

Traditionally, humans were dependent on the healing properties of medicinal plants and have been greatly used to cure human diseases in Asiatic countries. In recent years, due to low toxicity and side effect-free therapeutic performance, indigenous medicine has acquired considerable attention as an alternative drug. Moreover, the discovery of active ingredients of medicinal herbs has become important for the development of novel medicines.[1] One such active ingredient of medicinal herbs is cinnamic acid. Cinnamic acids have been identified across the world and have the widest range of biological functions. They are frequently found

in conjugated form or as partially or completely synthesized cinnamic acid conjugates. Cinnamic acids have been combined or conjugated with well-known medications among other reported methods, in an attempt to achieve either synergistic or multi-target effect.[2] They are found in apples, beetroot, tomatoes, coffee beans, pears, cereals, spinach, tea, citrus fruits, grapes, cinnamon, potatoes, cranberries, prunes, cloves, etc.[34]

There are two isomers of it: cis and trans where the latter being more prevalent. Because of its structure, which consists of an acrylic acid functional group, a double bond and a benzene ring, it is possible to alter the aforementioned functionalities with a variety of compounds to create bioactive agents with increased efficacy. The 3-phenyl acrylic acid functionality in cinnamic acid provides three main reactive sites such as, addition at the unsaturation, substitution at the phenyl ring and reactions of the carboxylic acid functionality. Because of these chemical properties cinnamic acid-derivatives, both traditional and modern synthetic agents received a lot of interest in the field of medical research.[5]

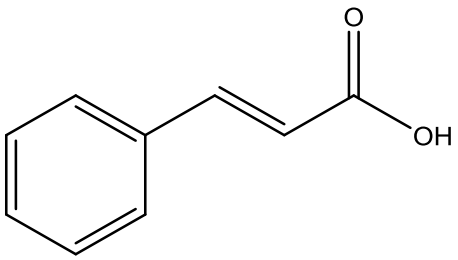

Figure 1: Structure of Cinnamic acid.

2. EXTRACTION

Cinnamaldehyde and cinnamic acid are the two main phytoconstituents found in cinnamon. **Hyun-Gyu Lee *et al.*,** studied that the Response Surface Methodology was used to optimize the extraction yield, time & energy consumption and CO_2 emission of these compounds during the microwave-method, ultrasound method and reflux method. It was found that the highest yield of cinnamic acid was obtained via the reflux method of extraction. Hence, the reflux method was preferred over the microwave method and ultrasound method for the extraction of cinnamic acid.[6]

Sri Wardatun *et al.*, used maceration, soxhlation and infundation in the extraction process. As a solvent, 50%, 70%, and 96% ethanol were utilized. The dry extract was produced by drying the liquid extract under vacuum. Trans cinnamic acid and cinnamon aldehyde were characterized by, spectrophotometric ultraviolet-visible methods. From the characterization, it

was found that the maceration method gave the highest yield of cinnamic acid (i.e. about 151.362 mg/g of dry extract) than that of soxhlation and infundation extraction methods.[7]

According to **Pramote Khuwijitjaru *et al.*,** the subcritical water extraction method was found to be more effective for extracting cinnamic acid and its derivatives than using an organic solvent (methanol). Subcritical water extraction at 200°C gave a greater yield of cinnamic acid than that of extraction via methanol.[8]

Nibal Kh. Mousa *et al.*, developed a method for extracting cinnamic acid using the TLC principle. The procedure involved mixing 150g of cinnamon bark powder with 2.5 Liters of methanol and letting it to stand for 72 hours in a cool, and dark area. Then, used a rotary evaporator to filter and dried the mixture at 30 to 40 ℃, obtaining 1/10 of the original volume and stored it at 20℃. The plant extract did not oxidize during any of these procedures since they were shielded from intense light and stress. Next, the powder was hydrolyzed with hydrochloric acid and extracted with chloroform. Then, the liquid-solid Column Chromatography technique (using a silica gel column) was used to separate the cinnamic acid, which produced a partially purified product that was eluted and separated as crystals using TLC method. About 10.5 mg of pure crystals were obtained from 150 grams of bark powder.[9]

Shuyun Shi *et al.*, used Magnetic porous molecularly imprinted polymers (MPMIPs) for extraction of cinnamic acid from apples. This method was found to be highly selective for extracting cinnamic acid.[10]

3. APPLICATION AND THERAPEUTIC ACTIVITIES OF CINNAMIC ACID

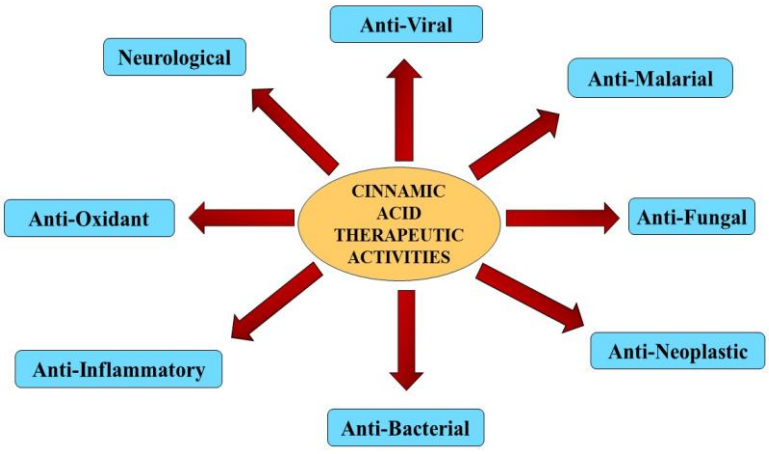

Figure 2: Therapeutic Activities of Cinnamic Acid.

It is easy to alter the aforementioned functions using a range of chemicals, producing bioactive agents with increased efficacy, because of their structural flexibility. The biological efficacy of cinnamic acid is significantly affected by the type of substituents added. Many of the cinnamic acid derivatives are extremely promising therapeutic agents because it has been shown that some of them are more effective in vitro than traditional medications used to treat infectious or chronic diseases. It has been found that derivatives of cinnamic acid are used to treat a variety of conditions.[11]

The various therapeutic activities of cinnamic acid are depicted in the figure 2.

Various Therapeutic Activities of Cinnamic acid are summarized in Table 1.

Table 1: Summary of Therapeutic Activities of Cinnamic acid and its derivatives.

Sr. No.	Cinnamic Acid or its Derivative/Composite	Mechanism	Indication	Reference
A. Anti-inflammatory activity				
1	Cinnamic Acid with Mangiferin	Reduction of IL-6, IL-12 and TNF-α levels	Rheumatoid Arthritis	[12]
2	Cinnamic Acid	Reduction of TNF induced Inflammation	---	[13]
B. Anti-oxidant activity				
3	Cinnamic Acid	Inhibition of Multiplication of *Helicobacter Pylori* by reducing Gastric HCl secretion and inhibition of cyclooxygenase enzyme.	Gastrointestinal problems, Amenorrhea and in some Cardiovascular disorders	[14]
C. Anti-bacterial activity				
4	Cinnamic Acid with Chlorogenic Acid	Active against *Alicyclobacillus acidoterrestris.* Disrupts the bacterial cell membrane leading to leakage of proteins and Nucleic acid leading to cell death.	---	[3]
5	Cinnamic acid	Active against *C.*	---	[15]

		albicans, *E. coli*, and *S. aureus*.		
6	Cinnamic acid with Quercetin	Active against fish pathogens	Treatment of fish	[16]
7	Cinnamic acid	Active against *M. tuberculosis*	Multi drug resistant tuberculosis	[17
8	Cis-cinnamic acid	Active against *M. tuberculosis*	Multi drug resistant tuberculosis	[18]
9	4-methoxycinnamic acid	Active against *Baccharis grisebachii*	---	[4]
10	Cinnamic acid with Harmine	Active against *P. berghei* and *P. falciparum* Inhibits erythrocytic and hepatic stages of Plasmodium infection	Malaria	[11]
D. Anti-diabetic activity				
11	Cinnamic acid	It increases insulin sensitivity and modifies gluconeogenesis and glycogenesis and also reduces blood glucose and enhances glucose tolerance	Diabetes	[19,20]
E. Peridonitis anti-inflammatory activity				
12	Cinnamic acid	It decreases osteoclast counts and inflammation and increases osteoblast counts and OPG expression	Peridonitis	[21]
F. Anti-viral activity				
13	Cinnamic acid	It inhibits Hepatitis C virus replication	Hepatitis C	[22]
G. Anti-fungal activity				
14	Cinnamic acid	It inhibits benzoate 4 hydroxylase which prevents fungal growth	---	[23]
H. Neurological activity				

15	Cinnamic acid derivatives	It inhibits cholinesterase	Alzheimer's disease	[24]
16	3-methoxy-4 hydroxycinnamic acid, 3-methoxy-4-acetamidoxycinnamic acid, and 3,4-dimethoxycinnamic acid	It inhibits the conversion of alpha-synuclein into amyloid, which can help treat Parkinson's disease	Parkinson's disease	[11]
Anti-neoplastic activity				
17	Cinnamic acid derivatives	It Shows cytotoxic effects	Breast, colon and cervical cancers	[25,26]
J.Anti-malarial activity				
18	1- (R)-phenylethyl aniline and cinnamic acid	It inhibits *P. falciparum*	Malaria	[27]

Anti-inflammatory activity

Inflammation is an immune response that can occur under the influence of pathogens, toxic compounds, damaged cells, etc. This ultimately leads to tissue damage or disease. Inflammation includes symptoms like swelling, pain, redness, etc.[28] Inflammation occurs under the influence of one of the most important mediators called Interleukins (IL). However, Interleukin-1 is a potent proinflammatory cytokine, which is produced by monocytes present in the blood. Interleukin-1b is a molecular form of interleukin-1 (IL-1). At low levels, IL-1 leads to fever, hypotension, and release of Adrenocorticotropic Hormone.[29]

Weijie Li *et al.*, identified that Mangiferin and cinnamic acid were found to be bioactive molecules that could reduce joint inflammation. This was found to be possible by inhibiting the inflammasome and modulating the pyroptosis. This combination reduced the arthritis severity and arthritis incidence. The level of inflammatory mediators like TNF-α, IL-6, and IL-12 is observed to be alleviated after the treatment with Mangiferin and cinnamic acid Hence, this combination was found to treat Rheumatoid Arthritis.[12] Tumour Necrosis Factor – α (TNF-α) acts as an inflammatory agent that regulates macrophage function, initiates inflammation and takes part in the proliferation, apoptosis, and differentiation of macrophages. It is rapidly released during infection and is found to play an essential role in the development of chronic inflammatory diseases.[30] According to **Xiaofei Li, Zhibin Wen**, and colleagues' research, cinnamic acid significantly reduced TNF-induced TNF expression in endothelial cells which prevented NF-KB activation.[13]

Anti-oxidant activity

Joohee Jung *et al.*, found that the ethanolic extract of *Cinnamomum ramulus* showed potent antioxidant activity, against *Helicobacter pylori* bacteria and has an acid-neutralizing capacity. These activities suggested that it is a potent anti-gastric drug. *Cinnamomum ramulus* is also used in treating cardiovascular diseases like thrombosis. Also used in the remedy of menstrual disorder, gastrointestinal disorder, amenorrhea etc. It inhibits the cyclooxygenase enzyme. Complete inhibition of *Helicobacter pylori* colony by ethanolic extract of *Cinnamomum ramulus* was observed and this effect was similar to that of ampicillin. The ethanolic extract showed antacid activity but it has low acid neutralizing capacity when compared with hydrotalcite. Oral administration of cinnamic acid reduced the HCl-induced gastric lesions in mice. The activity was either due to the stimulation of gastric mucus or the inhibition of cytotoxicity of HCl. Cinnamic acid significantly increased mucus secretion.[14] Hydroxyl derivatives of cinnamic acid provided significant relief from hypertension due to their antioxidant properties.[31]

Anti-bacterial activity

Rui Cai *et al.*, concluded that cinnamic acid and chlorogenic acid showed antibacterial activity against the *Alicyclobacillus acidoterrestris*. *Alicyclobacillus acidoterrestris* can be isolated from rotting fruits, such as grapes, apples, etc. It was more isolated from the apple. The cinnamic acid and chlorogenic acid caused disruption of the membrane which resulted in the leakage of proteins and nucleic acid. This resulted in the death of the bacteria. Among both more activity was showed by cinnamic acid. Therefore, its use was found in the fruit juice industry. The minimum inhibitory concentration of cinnamic acid was 0.375 mg $mL^{-1.}$ and minimum bactericidal concentration was found to be 0.50 mg mL^{-}.[13]

Houshang Afrouzan *et al.*, performed an antibacterial assay using Iranian propolis. Iranian propolis is a product of bees. It contains phenolic compounds, flavonoids, and terpenes. Cinnamic acid is a phenolic compound and its derivatives like caffeic acid were found in Iranian propolis. These constituents were found to show antimicrobial activity against *C. albicans*, *E. coli*, and *S. aureus*.[15]

Vinnakota Gangadhara *et al.*, found that cinnamic acid showed antibacterial activity against fish pathogens. This was due to the positive antibacterial interaction with quercetin and cinnamic acid. Hence, this combination of quercetin and cinnamic acid could be used to treat infections in fish.[16]

Nalin Rastogi *et al.*, found that cinnamic acid showed synergistic activity when given with anti-tuberculosis drugs like Isoniazid, Rifampin and other drugs such as Amikacin, Ofloxacin and Clofazimine. Also, such an increase in the activity of cinnamic acid made it possible to treat Multidrug-Resistant Tuberculosis.[17]

Yen Ling Chen *et al.*, found that cis-cinnamic acid exhibited more anti-mycobacterial activity as compared to that of trans-cinnamic acid and hence, used in treating Multidrug-Resistant Tuberculosis (MDR-TB). The combination of cis-cinnamic acid and first-line drugs like isoniazid or rifampicin showed a synergistic effect in the treatment of tuberculosis.[18]

Cinnamic acid exhibits stronger growth inhibition against one or more bacterial and fungal species, as do their esters, amides, aldehydes, and alcohols. A specific substitution pattern on the aryl ring of cinnamic acid has been created, and their antibacterial activity has been evaluated. The antibacterial activity of the compound, 4-methoxy cinnamic acid was evaluated after it was extracted from the Argentinean medicinal plant *Baccharis grisebachii*.[4]

Plasmodial Infections are caused due to plasmodium species. These parasites not only harm humans but also harm other mammals. Such parasites are transmitted by vectors usually mosquitoes. This leads to certain symptoms depending on the plasmodium species.[32] **Perkovic *et al.*,** synthesized harmine and cinnamic acid hybrids which were subjected to anti-plasmodial evaluation against the hepatic stage of *P. berghei* and the erythrocytic stage of *Plasmodium falciparum* (chloroquine-resistant PfDd2 strains and chloroquine-sensitive Pf3D7 strains), as well as cytotoxicity against HepG2 cell line. As compared to the parent compounds at the erythrocytic and hepatic stages of Plasmodium infection, harmine-cinnamic acid-derivative conjugation via triazole linker produced hybrids with excellent anti-plasmodial action.[11]

Anti-diabetic activity

Diabetes is a degenerative disease which can affect the organs like eyes, kidneys, etc. Diabetes is caused due to increased blood sugar levels which is also called hyperglycaemia. Diabetes can disturb the Cardiovascular system and hence diabetes patients have a higher risk of cardiovascular diseases. Hence, proper glycaemic control shall be essential for the management of diabetes.[33]

W. Arlt *et al.,* observed that in diabetic rats, cinnamic acid increases insulin sensitivity and modifies gluconeogenesis and glycogenesis.[19] It also reduced blood glucose and enhanced glucose tolerance, which implies that it likely acts by encouraging pancreatic β-cells to secrete insulin.[20]

A 2,4-TZD moiety may produce bifunctional compounds that interact with both the insulin receptor and PPAR to produce hypoglycaemic effects. By increase in peripheral tissue insulin sensitivity, especially in adipose tissue, TZDs function as PPAR agonists and reduced the risk of diabetes.[19]

5. Periodontitis anti-inflammatory activity

According to **Ozkan Karatas *et al.,*** there was a decrease in osteoprotegerin (OPG) expressions and osteoblast counts and an increase in PPAR-γ, COX-2, and RANKL levels, as well as osteoclast, counts in response to experimentally induced periodontal inflammation and bone destruction. In the animal model of periodontitis, cinnamic acid prevented periodontal inflammation with decreased osteoclast counts and inflammation and increased osteoblast counts and OPG expression.[21]

6. Anti-viral activity

It has been reported that several derivatives of cinnamic acid have antiviral properties. Through the induction of oxidative stress, derivatives of cinnamic acid significantly inhibited the replication of the Hepatitis C virus (HCV). **Ryota Amano *et al.,*** found that one of the derivatives of cinnamic acid have a strong anti-HCV effect.[22]

7. Anti-fungal activity

B. Koroš̆ec *et al.,* performed antifungal activity of cinnamic acid and its derivatives. It was found that seven cinnamic acid derivatives showed potent antifungal activity. They inhibited benzoate 4 hydroxylase which is particularly present in fungi and can be distinguished from other eukaryotes.[23]

Hazir *et al.,* showed that trans Cinnamic Acid (TCA) and *X. szentirmaii* metabolites have greater antifungal activity than metabolites obtained from a range of different *Xenorhabdus* or *Photorhabdus* species. They had antifungal qualities that might be applied as organic bio fungicides to combat plant fungal diseases.[34]

8. Neurological activity

Alzheimer's disease is a neurodegenerative disorder caused by dementia. Such a disease causes a reduction in thinking abilities and a reduction in doing various daily activities independently. This disease can be due to head injuries, aging, vascular diseases, infections, certain environmental factors, etc. However, genetic inheritance can also be a cause leading to Alzheimer's disease.[24]

Lan *et al*., created cinnamic acid-derivatives by reacting N-benzyl pyridinium with cinnamic acids of different substitutions. These compounds inhibited cholinesterase, providing a potential Alzheimer's disease treatment.[11]

According to **Medvedeva *et al*.,** 3-methoxy-4 hydroxycinnamic acid, 3-methoxy-4-acetamidoxycinnamic acid, and 3,4-dimethoxy cinnamic acid inhibited the conversion of alpha-synuclein into amyloid, which helped in the treatment of Parkinson's disease.[11]

9. Anti-neoplastic activity

A malignant or cancerous tumor that originates in the breast tissue is called breast cancer.[35] The anticancer potential of natural products as chemo preventive and chemotherapeutic drugs has been extensively studied. On tumor cells, it was discovered that cinnamic acid and its derivatives had cytotoxic effects. Compared to its derivatives, cinnamic acid exhibited reduced efficacy.[25] The derivatives of cinnamic acid killed colon and cervical cancer cells by inhibiting histone deacetylase.[26]

10. Anti-malarial activity

Using a peptide coupling process between derivatives of 1- (R)-phenylethyl aniline and cinnamic acid, a number of minor molecules have been successfully synthesized. The compounds have been studied against strains of P. falciparum that are resistant and sensitive to chloroquine.[27]

11. Other activities

Cinnamic acid is used as a flavouring agent, stimulant, carminative, antiseptic and insecticide. It has been used as a perfume in cosmetics for many years, and also have several therapeutic applications against degenerative diseases.[26] Melanin synthesis is mainly controlled by two enzymes: tyrosinase and dopachrome tautomerase. Cinnamic acid showed potent inhibitory effects on tyrosinase production and activity in Melan-a cells. Cinnamic

acid works as a depigmenting agent by inhibiting the initial step of the melanin production pathway.[36]

4. VARIOUS STRATEGIES FOR DRUG DELIVERY OF CINNAMIC ACID:

A formulation or device that facilitates the introduction of a medicinal material into the body and enhances its safety and efficacy by regulating the rate, time, and location of drug release in the body is called a drug delivery system. The human body can absorb drugs through various routes. They may be directed towards different organs and illnesses, or they may be meant to have systemic effects. The ailment, the desired outcome and the substance that is available all influence the choice of route of administration. Medication might be injected systemically and directed towards the diseased organ, or it can be delivered directly to the affected organ.[37]

Due to extensive interdisciplinary research combining contributions from chemistry, material science, engineering, pharmacology and other associated biological disciplines, the controlled-release in pharmaceutical sector has had the greatest growth. A controlled-release drug delivery system can improve the way drugs are delivered to the target organ and accomplish the following goals:

(1) Maintain the blood's optimal therapeutic drug concentration with minimal fluctuation
(2) Repeatable and consistent release rates for a longer period of time
(3) Prolong the duration of action for drugs with short half-lives
(4) Eliminate side effects, frequent dosage, and drug waste
(5) Optimize therapy and improve patient compliance.

Figure 3: Drug Delivery Strategies of Cinnamic Acid.

Many methods have been developed for drug delivery with controlled release, and some of them are currently available in the market. These include transdermal nitroglycerin delivery systems for preventing angina and oral osmotic pump devices for delivering various medications.[38]

Table 2: Various drug delivery of Cinnamic acid.

Sr. No.	Drug/Combination	Matrix for Drug Delivery	Drug Delivery Type	Reference
1	Trans-Cinnamic acid	Self-Nano Emulsion	Oral	[39]
2	Cinnamic Acid	Organoclay	Prolonged	[40]
3	Cinnamic Acid	Transferosomes	Transdermal	[41]
4	Cinnamic Acid	PLGA-Nanoparticles	Targeted	[42]
5	Trans-Cinnamic Acid	Nanoparticles	Transdermal	[43]
6	Cinnamic Acid-Berberine	Nanoparticle	Targeted	[44]
7	Cinnamic Acid Derivative	Fluorescent Nanoparticle	---	[45]
8	Cinnamic Acid	Gold Nanoparticles	Targeted	[46]
9	Doxorubicin	MPEG-Lys-Cinnamic Acid Micelles	Targeted	[47]
10	9-Nitro Camptothecin	PEG-Cinnamic Acid Micelles	Targeted	[48]
11	Cinnamic Acid Derivative	Liposomes	Targeted	[49]
12	Cinnamic Acid	Calcium Alginate	Topical	[50]
13	Cinnamic Acid Derivative-D, L Lactic Acid	4-hydroxycinnamic acid and Lactic Acid Biocomposite	---	[51]
14	Trans-Cinnamic Acid	Colon Targeted Carrier	Colon Targeted	[52]
15	Cinnamic Acid Derivative	Niosomes	Vesicular	[53]
16	Carbamazepine	Cinnamic Acid Co-former	---	[54]
17	Gemfibrozil	Trans-Cinnamic Acid Co-former	Prolonged	[55]
18	5-Fluorouracil	Cinnamic Acid Co-former	Targeted	[56]
19	Moxifloxacin & Cinnamic Acid	Crystal Adduct	Prolonged	[57]
20	Cinnamic Acid	Organogel	Organogelation	[58]

Cinnamic acid is delivered using a variety of drug delivery methods, including

Self-nano emulsifying drug delivery system

The drug, surfactant, co-surfactant, and oil mixtures that form the isotropic fine oil-in-water are known as self-nano-emulsifying drug delivery systems, or SNEDDS added to aqueous phases as an emulsion in mildly agitated conditions.[59]

Many food plants, fruits, and herbs contain trans-cinnamic acid (t-CA), also known as 3-phenyl-2-propenoic acid. It is a white, oily phenolic powder. It has been discovered that t-CA has antidiabetic effects. However, t-CA has a low water solubility, which limits its usefulness and low bioavailability. For this reason, a self-nano-emulsifying drug delivery system has been developed.

In their experiment, **Houyong Wang *et al*.,** used alloxan-induced diabetic rat model. 30% oil (isopropyl myristate), 10% co-surfactant (PEG 400) and 60% surfactant (Kolliphor EL) made the SNEDDS formulation. It was found that there was decrease in blood glucose level and increase in body weight of the rat models, after administration of t-CA suspension and SNEDDS.[39]

Prolonged drug delivery system

The Prolonged Drug Delivery System involves the release of the drug from the formulation for an extended period or prolonged period of time. Hence, the concentration of the drug in the plasma is maintained for an extended or prolonged period. This mainly helps in better patient compliance and reduction in the frequency of administration of doses.[60]

Ilaria Calabrese *et al*., had loaded cinnamic acid into the organoclay. This organoclay formulation showed prolonged release of cinnamic acid. In comparison to raw clay, the hybrid nanocarrier's surfactant incorporation allowed for a higher drug loading capacity and guaranteed the full release of the active ingredient i.e., cinnamic acid following oral drug administration. According to these findings, the prepared Organoclay was regarded as potentially useful materials for the creation of innovative drug delivery systems intended for the administration of cinnamic acid.[40]

Transdermal drug delivery system

The transdermal drug delivery system (TDDS) is a drug delivery method that delivers the medication via the skin at a predetermined and controlled rate. It provides a number of benefits, including better drug therapy elimination, avoiding first-pass metabolism, minimum adverse effects, enhanced bioavailability, prolonged therapeutic effect and better patient compliance. When administering medication through this method, several factors to be taken into consideration are skin age, skin condition, physicochemical parameters, and environmental conditions.[41]

According to the definition, transferosomes are specifically engineered vesicular particles with at least one inner aqueous compartment encircled by a lipid bilayer with properly tuned characteristics.[61] The cinnamic acid transferosomes when compared to regular liposomes, improved cinnamic acid's skin penetration, indicated that they are a highly effective transdermal drug delivery vehicle.[62]

Nanoparticles

The most common cause of cancer-related death in women is thought to be breast cancer. Breast cancer is categorized as triple-negative, hormone receptor-positive and overexpression of the human epidermal growth factor receptor-2 (HER2). The most aggressive and diverse subtype of breast cancer is known as triple-negative breast cancer. Triple-negative breast cancer tumors are characterized by a dynamic process called epithelial-to-mesenchymal transition (EMT), in which mesenchymal characteristics predominate over epithelial ones. As a result, focusing on EMT has become a viable cancer therapeutic option. Using the nanoprecipitation approach, a novel Cinnamic acid Polylactic-co-glycolic acid- nanoparticles (CIN-PLGA-NPs) delivery system was successfully created to enhance the biological effects of cinnamic acid on triple-negative breast cancer.[42]

Trans-cinnamic acid is a common ingredient in food, cosmetic, and pharmaceutical additives and exhibits strong antioxidant properties. However, trans-cinnamic acid has drawbacks such as low water solubility, which results in reduced bioavailability. For these reasons, trans-cinnamic acid was formulated in the form of nanoparticle. Hence, as the surfactant hydroxypropyl methylcellulose (HPMC), as the anti-solvent de-ionized water and as the solvent ethanol were used to prepare nanoparticle powder of trans-cinnamic acid. Trans-cinnamic acid nanoparticles' solubility, dissolution rate, antioxidant activity, transdermal penetration in vitro, and bioavailability were all much better compared to that of the raw trans-cinnamic acid.[43]

Many first-line antibiotics do not work on *S. aureus*. With the current antimicrobial agents, the "super bacteria" is hard to control. Nanotechnology is being applied more and more in the antibacterial field, indicating that nanotechnology holds great promise for creating novel and potent antibiotics. **Xuemei Huang *et al*.,** used this technology and developed self-assembled nanoparticles. Compared to certain first-line antibiotics like norfloxacin, amoxicillin, and tetracycline, the inhibitory effect of Cinnamic acid -Berberine nanoparticles (CIN-BBR NPs) on MRSA was significantly greater.[44]

A brand-new photosensitive and fluorescent nanoparticle was created. **Dongjian Shi *et al.*,** created the nanoparticle and was made of a derivative of cinnamic acid and Europium ions. The Eu3+-complexes' fluorescence characteristics were greatly improved. This new fluorescent and photosensitive nanoparticles found application as a fluorescence probe and carrier in optoelectronics systems, as well as in the biomedical and environmental domains.[45]

Gold nanoparticles

Because of their compact size, large surface area for drug loading and good cell penetration, Gold Nanoparticles (AU-NP) is a potential drug delivery vehicle. They also improve drug bioavailability and lower drug resistance by precisely focusing on cellular function. Gold nanoparticles when conjugated with cinnamic acid have been used in the treatment of amoebic and bacterial infections.[63]

Karthika Subramanian *et al.*, linked cinnamic acid to citrate-stabilized gold nanoparticles, which were then assessed against MCF-7 breast cancer cells. When applied to MCF-7 breast cancer cells, it was discovered to have a potent cytotoxic effect.[46]

Polymeric micelles as drug delivery system

Polymeric micelles are gaining significant attention as innovative colloidal delivery methods capable of meeting the demands of an optimal and adaptable drug carrier. Self-assembly of amphiphilic block copolymers in an aqueous medium resulted in the formation of polymeric micelles. Their structure is made up of a hydrophobic core that serves as a micro reservoir for encapsulating hydrophobic medicines, proteins, or DNA, and a hydrophilic shell that interfaces with biological fluids. These nanostructures are typically spherical. Polymeric micelles are superior to other colloidal delivery systems due to their core/shell structure's innate adaptability.[64]

Polymeric micelles were created using p–p conjugated cinnamic acid as a lipophilic moiety. The lipophilic structures known as MPEG CIN and MPEG–Lys–DCIN, which are amphiphiles with one or two cinnamic acid molecules, were created. The micelles contained the anticancer medication doxorubicin (DOX). Better stability and a higher drug-loading content have been shown by MPEG–Lys–DCIN micelles. Within the DOX-loaded micelles, a strong p–p stacking interaction was formed. The higher inhibition efficiency was shown in vitro and in vivo by DOX-loaded MPEG–Lys–DCIN micelles.[47]

To deliver the medication to the desired location, polymeric micelles were created. In this type of delivery mechanism, cinnamic acid was used with an anti-tumor medication such as camptothecin (9-nitro). Owing to the drug's low solubility in water, it was integrated into the micelles. Two molecules of cinnamic acid (lipophilic moiety) and one molecule of PEG (hydrophilic moiety) made up these micelles.[48]

Liposomes

The phospholipid vesicles, or liposomes, are spherical lipid bilayers that have the ability to entrap lipid molecules within the lipid bilayers or water-soluble solutes in aqueous domains of liposomal medication delivery systems target tissues.[65]

Cinnamic acid derivatives formulated as liposomes showed antileishmanial activity. The dimethylsulphoxide solution of 3,4,5-trimethoxycinnamic acid compound resulted in a reduction of leishmania. Standardized liposomal systems containing 3,4,5-trimethoxycinnamic acid drugs exhibited a negative surface charge which facilitated their interaction with parasite cells and compounds. Ultimately this resulted in an effective reduction of *L. amazonensis* culture.[49]

Microencapsulated drug delivery system

The majority of cosmetic products are made up of active chemicals in the form of emulsions, ointments, solutions, or powders. The mechanism by which many cosmetic products can cause alterations in the skin physiology through their delivery systems has been expedited by scientific advancements in both active carriers and chemicals.[66]

The term "cosmeceuticals" refers to a new product trend that has emerged from the usage of bioactive substances as ingredients in cosmetics. Because they are made with biologically active chemicals, cosmetics have benefits for the skin similar to those of pharmaceuticals. **Oludemi Taofiq *et al.*,** evaluated that cinnamic acid has been used in cosmeceuticals because of its anti-inflammatory, anti-tyrosinase, and anti-microbial properties. The compound's instability, sensitivity to pH and temperature, ease of degradation and low efficacy continued to be its issues for use in cosmeceutical formulations. Using calcium alginate as the matrix material, this compound was microencapsulated using the atomization/coagulation method in order to reap its benefits.[50]

Novel biodegradable copolymer

M. Matsusaki *et al.*, developed a unique functional biodegradable polymer. 4-hydroxycinnamic acid, a derivative of cinnamic acid, was polycondensed with D, L-lactic acid (DLLA). The copolymers were used in orthopaedics fixation materials, drug delivery system matrices, scaffolding for tissue engineering, and bone graft replacements. It was discovered that the copolymer had biodegradable properties, low toxicity, and biocompatibility.[51]

Colon targeted drug delivery

To improve the therapeutic effects and safety of medications, particularly for the treatment of colonic illnesses like inflammatory bowel disease (IBD), colon-specific drug delivery, or CSDD is utilized. The drug is eventually delivered to the target site with little loss in the upper intestine as a result of systemic absorption and pre-systemic metabolism. The advantage of this delivery technique is enhanced drug availability in the large intestine while decreasing systemic absorption of the drug. It was discovered that trans-cinnamic acid exhibited anti-inflammatory bowel disease activity (IBD). **Changyu Kang et al.,** employed a rat colitis model induced by dinitro benzenesulfonic acid and connected trans-cinnamic acid to the colon-targeted carrier. The anti-colitis effect of t-CA is enhanced when it is delivered to the colon.[52]

Niosomes

Trans ferulic Acid, or 4-hydroxy-3 methoxy cinnamic acid, is a hydroxycinnamic acid derivative that has some pharmacological properties and potential applications as an antioxidant, anti-inflammatory, and antimicrobial. Its solubility is poor, and it has low solubility and bioavailability. Hence, **Anahita Rezaei Roshan *et al.*,** developed vesicular drug delivery systems, or niosomes. The medication was more effectively delivered to the skin by this vesicular structure.[53]

Cocrystals

Cocrystals are a newly developed formulation technique in pharmaceutical drug development that aims to increase the stability, bioavailability, dissolution, and solubility of a variety of poorly water-soluble medications.[67] Co-crystals are materials that are crystallized and consist of two or more different molecules arranged in a single crystal lattice. These molecules are usually active pharmaceutical ingredients (APIs) and co-crystal formers, or "coformers".[68] The hot melt extrusion method (HME) was first used in the pharmaceutical

sector and is currently in widespread use. Currently, the HME method is employed for the co-crystallization process. Excellent coformer for the formation of cocrystals, cinnamic acid primarily interacts with its hydroxyl group through hydrogen bonding. **Hiren G. Moradiya *et al.,*** used the HME to prepare co-crystals of cinnamic acid and carbamazepine.[54]

Noopur Rathi and colleagues also synthesized curcumin and cinnamic acid cocrystals, given that curcumin's solubility is low despite its numerous advantageous characteristics. Because of their somewhat similar structures, curcumin and cinnamic acid promoted the growth of cocrystals. Together with curcumin demonstrating its advantageous properties. Cinnamic acid also demonstrated its own medicinal properties and enhanced the benefits of the cocrystals.[69]

Jessica Ribeiro Alves Silva *et al.,* synthesized Gemfibrozil and trans-cinnamic acid as a cocrystal. It is possible to use more stable and less soluble cocrystals for the design of pharmaceutical formulations with delayed or prolonged release as there may be no need to use matrices or polymers with pharmaceutical functions to modulate drug release. The lower dissolution of these cocrystals is related to changes in intermolecular interactions which resulted in a more stable crystalline structure and higher density.[55]

Farhan Jubeen *et al.,* also synthesized cocrystals. The 5-fluorouracil and cinnamic acid cocrystals were assessed in relation to HCT-116 colorectal cell lines. There was notable anticancer activity demonstrated by these cocrystals.[56]

Crystal adducts

Basanth Babu Eedara *et al.,* created a crystalline adduct of the anti-tubercular medication moxifloxacin and trans-cinnamic acid, which extended the drug's residence time in the lungs.[57]

Organogelators

Cinnamic acid is poorly soluble in water and can dissolve in oil due to the acrylic group that is joined to a benzene ring. Cinnamic acid may therefore have applications as an organogelator.[71] Organic liquids trapped in a thermo-reversible, three-dimensional gel network are known as organogels. Therefore, food scientists and industry managers are seeking ways to minimize oil migration in foods, reduce saturated and trans fats and

delivered bioactive molecules which have been drawn to organogels, a relatively new method for transforming liquid oils into structured systems.[58]

5. FUTURE PROSPECTS

Numerous medicinal properties were demonstrated by cinnamic acid and its derivatives, according to the investigations. Among many other things, it has anti-inflammatory, anti-diabetic, anti-oxidant, and antibacterial properties. In order to reap the benefits of cinnamic acid, further in vivo studies and clinical trials should be conducted in view of the fact that some of its effects were observed in vitro. Using Cubosomes to administer the medication is one of the unique approaches. Cubosomes can be used as a vehicle for cinnamic acid in future research. Since cinnamic acid has anti-neoplastic properties, it can be further utilized by encapsulating it in phytonanoparticle form. Thus, the use of cinnamic acid is essential in the current era of the pharmaceutical and medical industries, and it will have the chance to influence the development of novel drug delivery methods in the future by generating more innovative research.

Declaration of competing interest

The authors declare that any known competing financial interests or personal relationships could have influenced none of the work reported in this study.

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