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Exploring Therapeutic applications of Cinnamon oil and its microemulsion: A Comprehensive Review

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ABSTRACT:

This comprehensive review delves into the therapeutic attributes of cinnamon oil and its potential applications through the formulation of microemulsions. Derived from *Cinnamomum verum*, cinnamon oil has a rich history in traditional medicine due to its diverse array of bioactive compounds. This review underscores the imperative role of cinnamon oils in medicinal therapy encompassing radioprotective attributes, enzyme activity inhibition, as well as antimicrobial, anti-diabetic, antiinflammatory, and anticancer activities. Microemulsions, recognized as thermodynamically stable colloidal systems, emerge as pivotal vehicles for augmenting the solubility, stability, and bioavailability of lipophilic compounds intrinsic to cinnamon oil. A significant aspect elucidated is the potential synergistic effects arising from the integration of cinnamon oil with microemulsion technology, a synergy that not only enhances efficacy but also facilitates targeted delivery of therapeutic agents. The conclusions underscore the prospects of cinnamon oil-loaded microemulsions as an innovative therapeutic modality. The amalgamation of traditional wisdom with contemporary pharmaceutical formulations presents a comprehensive perspective on leveraging the therapeutic potential of cinnamon oil across various health applications. Future directions are explored, paving the way for sustained investigations into cinnamon oil and microemulsion formulations within the domain of therapeutic interventions.

Introduction

The formulation and characterization of plant essential oil-based microemulsion systems represent a cutting-edge exploration in the realm of pharmaceutical research, offering novel avenues for drug delivery and therapeutic applications. The significance of this study extends beyond the laboratory, aiming to address the pressing challenges in drug delivery and therapeutic efficacy. The Multidrug resistant bacteria derived diseases are currently regarded as the most significant challenge encountered by the pharmaceutical and nutraceutical industries because they are is time-consuming, expensive, and complicated methods to detect and treat the associated infections (1). Cinnamon bark, with its historical significance and proven medicinal attributes, serves as an ideal candidate for exploration in the context of microemulsion systems. The potential benefits span diverse applications, including the pharmaceutical, cosmetic, and food industries, aligning with the increasing demand for natural and sustainable solutions. Achieving a delicate balance in these microemulsion systems is paramount to their success, ensuring not only stability and precision in drug delivery but also harnessing the synergistic therapeutic effects of the bioactive compounds of cinnamon bark. (2) From enhancing drug solubility to providing stability in formulations, the cinnamon bark essential oil-based micro emulsions stand poised at the intersection of tradition and innovation.By unlocking the therapeutic potentials hidden within these microemulsions, the aim is to contribute to the ongoing evolution of pharmaceutical science, fostering a future where natural remedies are seamlessly integrated into modern therapeutic approaches.

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Essential oils

Essential oils (EOs) are naturally occurring oils extracted from various plant components and parts. They are natural, aromatic, and volatile liquid solutions. EOs are combinations of molecules obtained from spices that provide flavour and fragrance. The phrase "essential oil" today refers to fatty molecules or hydrophobic oils that have been derived from plants (3). In the preservation of food, essential oils play a crucial role by inhibiting the growth and dissemination of microbes. Furthermore, these oils find application in the production of soaps, toiletries, and even insect repellents (4). The alleged medicinal properties, such as antifertility, antidiabetic, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic, and diaphoretic attributes of these plant extracts, are incorporated into certain well-established contemporary medicinal treatments (5). Several methods such as expression, extraction, fermentation, and steam distillation are employed to extract EOs. To extract EOs via steam distillation, the plant materials from which the EOs are to be extracted must first be charged before being exposed to steam (6). The extraction of EO varies among the various parts of plants. Different compositions are stored in flowers, leaves, roots, seeds, stems, and other plant components. Highly sensitive technologies are needed for component identification and quantification. Different sites and environmental circumstances might result in distinct part substances in plants (7)

Microemulsions:

A microemulsion may be easily developed with droplet diameters between 100nm and 600nm. Compared with macroemulsions, microemulsions are thermodynamically stable and optically clear (transparent). Minimal interfacial tension (almost zero), an extensive interfacial area, and negligible interfacial free energy are characteristics of microemulsions (9). Microemulsions offers a wide range of industrial uses.As elucidated by Kreilgaard *et al.,* (10) and Trotta *et al.,* (11) in the realm of drug delivery vectors, microemulsions offer numerous advantages. These include increased penetration of hydrophilic, hydrophobic, and amphiphilic substances enhanced drug dissolution and resistance against hydrolysis by enzymes, advantageous modification of the therapeutic activity of drugs, increased absorption facilitated by surfactant-induced permeability, improved bioavailability of hydrophobic drugs and elevated mobility. Biodegradability and low toxicity are essential characteristics for surfactants. Three types of surface-active chemicals are used to stabilize microemulsion systems: zwitterionic, ionic and nonionic. Non-ionic surfactants, such polysorbate (Cremophor EL, Tween 20, Labrasol and Tween 80) are often employed by researchers in formulations owing to their low toxicological levels and innocuous character. The cosurfactants polyethylene glycol, isopropanol, ethanol, phosphatidylcholine, and diethylene glycol monoethyl ether can be incorporated into the microemulsion formulation for better versatility at the interface (12).

The organic phase of microemulsion systems is made up of oils. Oils interact with the hydrophilic part of the surfactant to solubilize therapeutic molecules. Fatty acid chains and triglycerides and mixed glycerides, which are made up of mono, di, and triglycerides are the primary constituents found in oils. The long-chain triglyceride oil types are not suitable for the formulation of microemulsion. In spite of these findings, monounsaturated fatty acids and fatty acid esters have also been widely employed for ME production as hydrophobic phases because their properties promote their penetration. These oils do not offer any aroma or aesthetic value to the formulation and are pharmacologically inactive, irritating, and poisonous in nature (13). The cumulative effect on the fluctuation in the amount of free energy during the formulation of a microemulsion is the result of the sum of the energy required to construct a novel oil/water interfacial area and the modification in configurational entropy that occurs throughout the process of dispersion. Microemulsions occur naturally without the need for energy input (14).

Formation of Microemulsions:

Pseudoternary phase diagrams are frequently employed to identify the exact oil-surfactant-water concentration ranges required for the formation of MEs since it is difficult to anticipate ME formation on the basis of the complicated physical-chemical interactions between components (15). An oil, surfactant, and water mixture can create a wide range of formations and phases. Many of these structures and stages are clearly recognized by visual inspection on the basis of their physical

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characteristics. Emulsions are opaque, and the water and oil phases will ultimately split. Lamellar structures and cubic phases have relatively high viscosities, and polarised microscopy may be used to determine the crystalline phases (16).

The interface in the MEs fluctuates regularly and on its own. Microemulsions are dynamic systems, and the components that collectively make them up have significant effects. The physiochemical characteristics of the constituent parts as well as their relative proportions can have an impact on the structure of ME system as illustrated in Fig. 1. Since they are stable, simple to manufacture, and have a high capacity for an extensive range of drug solubilization, including lipophilic and hydrophilic molecules in a single formulation, monophasic microemulsion given focus as a possible drug delivery vehicle. (17). Thermodynamic stability (extended shelf life), ease of manufacture (zero interfacial tension and almost spontaneous creation), low viscosity with Newtonian behaviour, and high solubilization capacity are all parameters that MEs can satisfy. MEs were selected as the optimal liquid drug delivery vehicles since the tiny droplets have an enhanced ability to bind to membranes and deliver bioactive compounds in a more regulated manner (18). In the past two decades, a variety of researchers have investigated ME due to to their enormous potential in several applications. A great deal of progress has been made as a result of the complex phase behaviour and intriguing microstructures in ME forming systems (19).

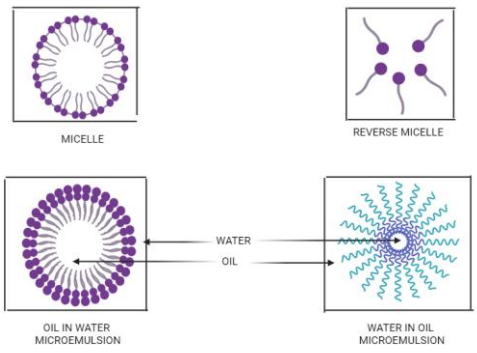

Fig. 1 Types of Microemulsion

Cinnamon:

Since very early times, cinnamon has been utilized for a variety of reasons. Since the 16th century, cinnamon has been used as a culinary spice and to keep food from unfit for consuming. It is widely used for aromatherapy, fragrance, cooking and bakery purposes. Additionally, it has medical applications for treating gastric ulcers, stomach distress, diarrhoea, and other conditions. Cinnamon bark is an exemplary element to treat type 2 diabetes and to reduce blood cholesterol. It may also have an insulin-potentiating effect (20). Owing to the presence of a vascular-thinning component that helps reduce and eliminate inflammation, the oil is used in aromatherapy as a massage therapy to increase blood circulation. Cinnamon oil is especially efficient in producing a soothing and rejuvenating impact on the mind, body, and spirit because of its pleasant fragrance. It may be used to ease hypertension, as well as a room refresher, and is often employed in potpourris (21)

Despite the fact that there are up to 250 distinct Cinnamomum species, only eight have been found to be significant from a cultural or economic standpoint. The cinnamon species included *Cinnamomum burmannii Cinnamomum zeylanicum, Cinnamomum iners, Cinnamomum cassia, Cinnamomum pauciflorum, Cinnamomum sulphuratum, Cinnamomum. assamicum and Cinnamomum bejolghota* are grouped as Ceylon cinnamon or real cinnamon (22). Each species generates an essential oil with a slightly distinctive composition and aroma. Commercial production of cinnamon includes only *C. zeylanicum* (Ceylon cinnamon) and *Cinnamomum cassia,* with Ceylon cinnamon generally being the most sought-after and expensive due to its delicate flavour and low coumarin content. (23) Other sources claim that ground cinnamon comprises ash, protein, fat, moisture, carbohydrates, and fiber. In addition, it comprises lipids, vitamins K, B, A, E, and C. Depending on the region of origin and the subsequent processing techniques, the composition differs (24)

Cinnamomum zeylanicum trees are tall, thin evergreens that may grow to a height of 65 feet. Every part from the tree is known to possess therapeutic potentials (Fig.2). Three to four years after planting, the inner cambium of immature to mature trees is removed for its cinnamon bark. Trees are frequently chopped to reduce height for easier harvesting and to promote the lateral development of branches that produce quills. Quills, which are approximately 10mm thick curls of bark, are removed and left to dry. The cambium is where essential oil sacs are found, and their sizes typically range from 2 to 10

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microns. The typical yield of essential oil from cinnamon bark is between 1% and 4% (25)

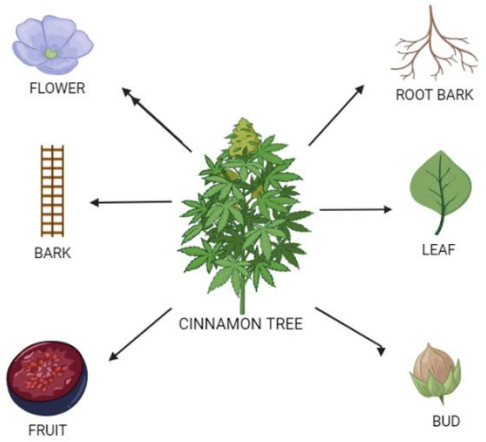

Fig.2 Distinctive Parts of the Cinnamon Tree for Extracting Essential Oils

Several investigations have employed cinnamon bark powder, which has very little cinnamon essential oil; however, exploring the medicinal benefits of concentrated and isolated cinnamon essential oil has drawn additional interest. It is crucial to assess the likelihood of such risks since the risks related to elevated daily consumption of cinnamon are not known (26).

Radioactive Properties:

Gamma radiation at fractionated dosages was administered to the rats. Before radiation treatment commenced, cinnamon extract was taken every day, and it was removed after radiation exposure. The findings showed that administrating cinnamon extract to radiation-exposed rats dramatically decreased the activities of glutathione peroxidase, catalase, superoxide dismutase and decreased glutathione levels which ends up in alterations in the antioxidant system of liver. Compared with those in rats that received radiation, the indices of protein and lipid oxidation and peroxidation in the liver were much lower. Additionally, alterations in the xanthine oxidoreductase system were greatly reduced. Additionally, there were significant improvements in the levels of tumour necrosis factor-alpha, C-reactive protein and hepatic nitric oxide. According to the results of this study, the injection of cinnamon extract significantly protected against radiation-induced oxidative and inflammatory damage (27).

Inhibition of enzyme activities:

Tyrosinase activity was examined when *Cinnamomum zeylanicum* oil was detected in progressive amounts, and the results revealed a very distinct pattern of behaviour. Compared with the control mixture, the reaction mixture took longer to turn red. After precipitation, the samples enriched *Cinnamomum zeylanicum* oil demonstrated a diminished melanin flake production. Melanin could only be recovered from the control studies; in contrast, when *Cinnamomum zeylanicum* oil was present, the recovery was minimal or non-existent (28).

The phenolic component content of Cinnamomum cassia may be the reason for the elastase activity inhibition caused by the methanolic extract of this plant at different concentrations. Additionally, the essential oils from Cinnamomum verum, which mostly consist of eugenol and cinnamaldehyde, have been found to have reduced elastase activity. Aging is a result of the deterioration of the elastin and protein matrix caused by increase in collagenase activity (29). It was also reported that the inhibitory activity of Cinnamomum zeylanicum with respect to collagenase was 35%, 25%, and 30% in the cases of essential oil extracts, aqueous extracts and methanol extracts respectively. It has been hypothesized that the synthesis of collagenase type I, which intensifies the activation of IGF-1, may be responsible for the modest inhibition of collagenase by cinnamon essential oil from *Cinnamomum zeylanicum* (30).

Using laboratory-based tyrosine kinase analysis, innovative angiogenesis inhibitors in plant-based diets were sought. The polyphenol-rich cinnamon extract substantially suppressed the kinase activity of the isolated VEGFR2. SU5416, an effective antagonist of VEGFR2, was employed as a positive control. Higher concentrations of the extract were required for the expression of VEGFR2 in endothelial cells than the dose used to lower the kinase activity of pure VEGFR2 in vitro. This may have occurred because the components of the active extract were unable to proliferate in culture or efficiently enter cells to demonstrate their effects. This finding suggested that by blocking the signalling pathway that VEGFR2 controls, cinnamon extract is a potent angiogenesis inhibitor. The spices that showed the greatest inhibitory effects on intestinal ATPases were

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clove and cinnamon. Studies showed that the main volatile constituent in cinnamon is cinnamaldehyde. These findings imply that cinnamon's main active ingredient (or ingredients), possibly cinnamaldehyde, can dissolve more readily in ethanol than in water (31).

Anti- diabetic activity:

For the treatment and prevention of metabolic syndrome and diabetic symptoms, cinnamon bark and cinnamon essential oil are both reported to be effective. The potential of aqueous cinnamon extracts to enhance insulin activity and boost insulin sensitivity is very promising. However, it was reported that cinnamon oil and the majority of its constituents, including cinnamaldehyde, do not exhibit in vitro insulin-enhancing activity in epididymal fat cells, indicating that the water-soluble polyphenols in cinnamon extract rather than the aromatic compounds in essential oils are responsible for the above activity (32).

Cinnamon in addition to vinegar or acetic acid might lessen the postprandial blood glucose response. It was assumed that there may be an additive impact as a result of the combination of these chemicals. The substantial effects of acetic acid and cinnamon on blood sugar levels and appetite immediately following eating demonstrated that these two substances may work in conjunction. Higher dosages of acetic acid and cinnamon ought to be explored further since they may have a more apparent additive effects on appetite or blood sugar levels (33).

Anti-inflammatory activity:

Several investigations have proven that cinnamaldehyde has beneficial effects on the circulatory process. Cinnamophilin is one of the prominent lignans found in Cinnamon philippinensis, and trials performed in 1994 by Yu and his associates showed that it might block the TXA2 (thromboxane A2) receptor in guinea pigs and rats. Given its dual function as a feasible thromboxane synthase inhibitor and TXA2 receptor antagonist, cinnamonophilin may be beneficial in the treatment of conditions associated with TXA2, especially in platelet aggregation (34). It seems that cinnamon extract lowers the levels of inflammatory markers in intestinal cells, which decreases circulating triglyceride-rich lipoprotein levels and reduces intestinal insulin resistance. The rats and hamsters that had been given fructose received treatment with cinnamon aqueous extract. The administration of this cinnamon extract reduced the overproduction of the lipoprotein apoB48 and the levels of blood triglycerides.

Additionally, in vitro cinnamon extract promoted the expression of insulin receptors and suppressed the excessive production of sterol regulatory element binding protein 1c (SREBP1c) and certain lipoprotein metabolism protein (MTP) genes. According to the authors, cinnamon extract can reduce postprandial hyper triglycerides and excessive apoB48 synthesis by improving insulin sensitivity and controlling 18 genes that are involved in lipid metabolism and insulin signalling (35).

Antimicrobial activity:

The impact of nonionic surfactants on the bacterial cytoplasmic membrane is one potential mechanism for the antibacterial action of cinnamon bark oil microemulsions. Owing to the presence of surfactants, microemulsions can significantly reduce the hydrophobicity of bacterial cell surfaces. As a result, DNA and RNA are released into the extracellular environment. Surfactants can also alter the cellular membrane's structure and shape and destroy the surface of bacterial cells (36). Better oil droplet dispersion in microemulsion owing to the presence of surfactants is another potential mechanism for boosting antimicrobial activity in the emulsion systems. As a result, more bacterial cell-oil droplet interactions are anticipated. The greater antibacterial activity of the microemulsions may be explained by the smaller droplet size (37).

According to Wang et al., (38) and colleagues, the formulated microemulsion's antimicrobial action is achieved by an inhibitory mechanism that alters and undermines the integrity of the cell membrane. An increased rate of cell death and the loss of intracellular ions, proteins, nucleic acids, and other chemical substances were the outcomes of the interaction between the microemulsion system and the cell membrane. The above alteration in membrane permeability and integrity was evident in the growth curve, showcasing a macroscopic inhibitory effect on the growth of both fungal and bacterial species. Protein and nucleic acid leakage followed by relative conductivity were among the factors that were used to gauge how severely a microemulsion degrades the membranes of bacteria and fungi as illustrated in Fig.3

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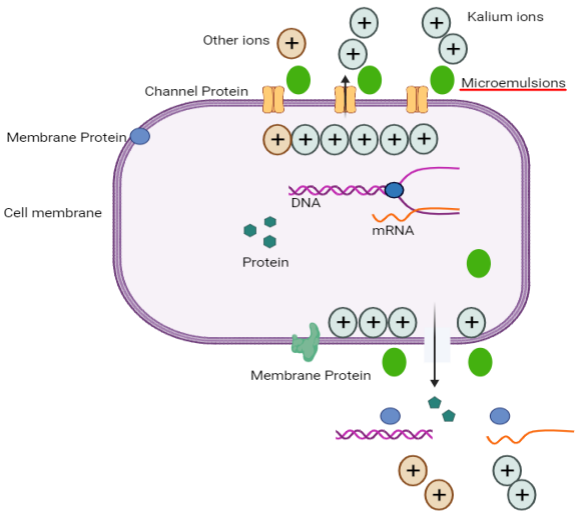

Fig.3 A schematic diagram showing the mechanism of antimicrobial activity of microemulsions

The high antibacterial activity of Cinnamomum verum oil against clinical pathogens was demonstrated by Mayaud et al., (2008) (39). Antibiotic-susceptible and antibiotic-resistant isolates had equal MIC values. Acinetobacter baumannii test strains were sensitive to cinnamon bark oil. Additionally, Cinnamon zeylanicum oil has a strong inhibitory action effect on bacteria isolated from individuals experiencing oral infections, according to Fani and Kohanteb's findings. Using the agar dilution technique, the MIC values for cinnamon oil were greater for methicillin-resistant Staphylococcus aureus and lesser for Streptococci that are resistant and non-resistant to multiple drugs. Cinnamon oil was shown to be very active against both multidrug-resistant and non-multi drug-resistant Streptococcus mutans at different concentrations creating zones of inhibition. The least active concentration of this oil for other microorganisms tested (40)

It was elucidated that the main respiratory pathogens Streptococcus pneumoniae and Streptococcus pyogenes were both susceptible to the antibacterial actions of oil extracted from cinnamon bark (41). Cinnamon bark oil had the most potent antimicrobial properties among the 11 essential oils tested for antibacterial against bacterial species such as *Pseudomonas jessenii, Shewanella putrefaciens, Aeromonas veronii, , and Acinetobacter johnsonii* (42).

ANTI CANCER ACTIVITY:

An assessment of the cytotoxic activity of Cinnamomum zeylanicum by employing the MTT assay to evaluate cell viability in both cancerous and normal cell lines. 5RP7 cells (H-ras active-rat fibroblasts) and F2408 cells (normal rat fibroblasts) were subjected to essential oil, and the viability of these cells was measured and expressed in terms of relative absorbance in comparison to that of the control cells. The researchers reported concentration-dependent inhibition of both cell lines after 24 and 48 hours of exposure to the essential oil from C. zeylanicum. The essential oil exhibited notable cytotoxicity in both cell lines, and this cytotoxicity was deemed significant. There was no time-dependent cytotoxicity when the oil was introduced to normal F2408 cells throughout a range of periods. At 48 hours after treatment, H-ras activated 5RP7 cells were more negatively impacted than the other groups were. After 24 and 48 hours of treatment, the viability of 5RP7 cells decreased. These results suggest that specific oil constituents might hinder ras transformation (43).

The cytotoxic effect of cinnamon oil on fibroblasts cells were also assessed in recent studies where the fibroblasts were seeded and allowed to adhere for 24 hours before they were exposed to cinnamon oil at various concentrations. Using a microplate reader, absorbance at 570 nm was determined and interpreted as a percentage of the viability of cells. There was little variance in the viability of fibroblast cells exposed to 10 and 100 µg/mL cinnamon essential oil over the course of 24 hours compared with that of control group. On the other hand, higher dosages (150, 200, and 400 µg/mL) on the other hand, significantly decreased the viability of the cells(44).

Conclusion

Our nation boasts a rich heritage of spices, drawing historical attention from invaders keen to understand their properties. Among these spices, cinnamon bark holds particular significance in our daily culinary practices, offering not only flavor but also a reservoir of hidden therapeutic benefits. The development of a cinnamon bark microemulsion has unveiled its diverse therapeutic properties, presenting promising prospects as a potent medicinal agent for humanity's welfare. Encapsulating cinnamon oil within a formulation of water and surfactant has not only preserved but also

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augmented its physicochemical and biological attributes, marking a novel approach towards enhancing substance properties. Such endeavors align with our aspirations for reliable solutions and are poised to significantly contribute to the attainment of Sustainable Development Goals in the near future.

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