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CHEMISTRY AND BIOACTIVITY OF CINNAMALDEHYDE: A NATURAL MOLECULE OF MEDICINAL IMPORTANCE

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ABSTRACT: Cinnamaldehyde is derived from the cinnamon essential oil (EO) having many biological and pharmacological significance. This review article explains the source, chemistry, physico-chemical characteristics of the molecule. The synthesis of its different analogous has been duly highlighted. The different applications narrating the various usage have been reported. It is expected that this review shall serve as a base material for future research in various directions.

INTRODUCTION: Antimicrobial capability is the destruction of the microorganism or the suppression of their multiplication or growth. On the other hand, an antimicrobial agent is the agents that possess these antimicrobial properties. It can be in the form of heat, radiation or a chemical interaction with the microorganism which may cause the disease. The antimicrobial activities are determined and compared by different types of test such as serial dilution (for example; MIC) and agar plates (for example; MBC) method. Both methods usually use model bacterium *Escherichia coli* (*E.coli*) in order to identify the antimicrobial active compounds¹.

E.coli is a common experimental bacterium to test many antimicrobial agents. *E.coli* bacteria normally live in the intestines of healthy human and animals. Most varieties of *E.coli* are harmless or may cause relatively mild diarrhea². However, in some strains, such as *E.coli* O157:H7 may cause severe abdominal cramps, bloody diarrhea and vomiting³.

It can be transmitted *via* contaminated water or food especially raw vegetables and undercooked ground meat. Healthy adults usually recover from *E. coli* O157:H7 infection within a week, but pediatric and geriatric individual have a greater risk of developing a life-threatening form of kidney failure called haemolytic uremic syndrome³. Consequently, inhibition of bacteria growth is necessary to prevent infection. The growth of bacteria *E.coli* is reported to be inhibited by cinnamaldehyde from cinnamon bark⁴. Cinnamon is a spice obtained from the inner bark of several trees from the genus *Cinnamomum* that is used in

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both sweet and savoury foods. Cinnamon is a bushy evergreen tree, cultivated as low bushes to ease the harvesting process. The leaves are long, leathery, shining green on upper surface when mature. Then, inside of cinnamon bark trees containing the chemical name cinnamaldehyde. An example of *Cinnamomum* species is indicated in **Table 1** with the references of previous studies. Cinnamaldehyde is the organic compound that gives cinnamon its flavour and odour (also known as cinnamic aldehyde)⁵. This organic compound is crucial to inhibit bacteria growth. Some of the *cinnamomum* species have been rigorously tested in term of their chemical composition, applications as bactericidal, antimicrobial, anticancer and also in food technology applications⁶.

Furthermore, the purity between cinamaldehyde (CIN) and trans-cinnamaldehydeas (TC) is slightly different⁷. The trans-cinnamaldehyde is more pure consisting <99% than cinnamaldehyde (unsaturated cinnamaldehyde) 98%. The synonyms of trans-cinnamaldehyde are (E)-Cinnamaldehyde, 3-Phenyl-2-propenal, 3-Phenylacrolein, 3-Phenylpropenal; Cinnamyl aldehyde, or Cinnamic aldehyde⁸. The solubility of this compound in water was low⁹⁻¹⁰.

So, it needs to undergo emulsification (o/w) to stabilize it¹¹⁻¹³.

Nanoemulsions (NEs) can be defined as a fine oil-in-water dispersions, having droplets covering the size range of 100–600 nm¹⁴. Nanoemulsion emerged from extensive nanotechnology studies for a novel drug delivery system (NDDS)¹⁵⁻¹⁶. Besides, nanoemulsions are also known as nano sized or submicron emulsions (SME), consists of systems with at least two nearly immiscible fluids dispersed one into another in the form of droplets with diameter lower than one micrometer¹⁵. The preparation of nanoemulsion is consisting of two methods such as low energy (phase inversion temperature, emulsion inversion point, Spontaneous emulsification) and high energy method (high-energy stirring, high pressure emulsification, Ultrasonic)¹⁴.

The purpose of this article is to provide an overview of the recently published data on the antimicrobial activity of essential oil is containing cinnamaldehyde that is considered suitable for application in numerous food industry fields especially as an antimicrobial agent¹⁷⁻¹⁹.

TABLE 1: LIST OF CINNAMOMUM SPECIES WITH THEIR REFERENCES OF PREVIOUS STUDIES

Botanical name (<i>Cinnamomum</i> species)	Research studies	References
<i>Cinnamomum zeylanicum</i>	Antimicrobial activity by using vapor-phase approach	Lopez <i>et al.</i> , 2005
	Cytotoxicity, Antimicrobial activity	Unlu <i>et al.</i> , 2010
	Antimicrobial activity by using tube dilution method	Gende <i>et al.</i> , 2008
	Reduction of clindamycin resistance of bacteria	Shahverdi <i>et al.</i> , 2007
<i>Cinnamomum osmophloeum</i>	Review: describe pharmacological of cinnamon in preclinical & clinical	Jakhetia <i>et al.</i> , 2010
	Antibacterial activity, Medical purposes	Chang ST <i>et al.</i> , 2001
	Chemical composition, Mosquito larvicidal activity	Cheng SS <i>et al.</i> , 2004
	Antifungal activity	Cheng SS <i>et al.</i> , 2006
<i>Cinnamomum cassia</i> (<i>C. aromaticum</i>)	Antifungal activity	Wang <i>et al.</i> , 2005
	Beef diet	Cardozo <i>et al.</i> , 2014
	Fumigant toxicity, Antifeedant	Huang <i>et al.</i> , 1998
	Induction of an apoptosis	Ka <i>et al.</i> , 2003

Cinnamaldehyde characteristics:

Structure:

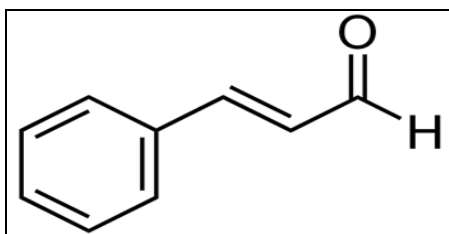


FIG. 1: CHEMICAL STRUCTURE OF CINNAMALDEHYDE, C₉H₈O

Cinnamaldehyde molecular formula was determined in 1834 by French chemists Jean Baptiste André Dumas (1800–1884) and Eugène Melchior Péligot (1811–1890)²⁰. It was isolated from cinnamon essential oil in 1834 and synthesized in the laboratory by Chiozza in 1854²¹. The natural product of *trans*-cinnamaldehyde molecule consists of a phenyl group attached to an unsaturated aldehyde²². As such, the molecule can

be viewed as a derivative of acrolein²³. Cinnamaldehyde is also known as β -phenylacrolein, due to the planar structure (fig. 1) and consist of the large number of π bond²⁴. The increase of transition with acrolein makes it change to visible band and produce the color of the compound²⁵.

Composition: Cinnamon contains essential oils and all other compounds such as cinnamic acid, cinnamaldehyde and cinnamate²⁰. Cinnamaldehyde is the major component comprising 85% in the essential oil and the purity of cinnamaldehyde in use is high (> 98%). Both oil and pure cinnamaldehyde are equally effective in inhibiting the growth of various microorganism such as Gram-positive and Gram-negative (*E. coli*) bacteria, and fungi including yeasts, filamentous molds and dermatophytes^{1, 26}. Their minimum inhibition concentrations (MIC) values as determined by agar dilution method varied only slightly. The MICs range of both oil and cinnamaldehyde for bacteria is large. The antimicrobial effectiveness of oil and its major constituent is comparable and almost equivalent, which suggests that the broad-spectrum antibiotic activities of oil are due to cinnamaldehyde²⁷.

Synthesis and formulation: There are several methods of laboratory synthesis of cinnamaldehyde is available, however it is most economically obtained from the steam distillation of the oil of cinnamon bark^{2, 28}. The compound can be prepared from the related compounds such as cinnamyl alcohol, (the alcohol form of cinnamaldehyde), but the first synthesis from unrelated compounds is the aldol condensation of benzaldehyde and acetaldehyde. In the cases of Bhanage *et al.*, 1999, methyl-trans-cinnamaldehyde and cinnamaldehyde selectivity towards unsaturated alcohol reached 96% and 93% respectively high in supercritical carbon dioxide (scCO₂) as a good solvent for selective production by hydrogenation.

Further, the selective catalytic hydrogenation of cinnamaldehyde to cinnamyl alcohol using Ru-modified and Y zeolite catalysts have been reported³⁰. An appropriate selection of bases and added salts can provide an efficient and straightforward route for the palladium-catalyzed synthesis of cinnamaldehydes from acrolein diethyl acetal and a

variety of aryl iodides or bromides¹⁹. This process allows the incorporation of many important functional groups such as aldehyde^{19, 31}.

Furthermore, cinnamaldehyde exhibits their antimicrobial activity clearly after emulsification because this chemical is slightly soluble in universal solvent (water). So, cinnamaldehyde emulsion needed to be stable during the storage so to elucidate its activity³². In the previous work, nanoemulsions were prepared using the spontaneous emulsification mechanism which occurs when an organic phase and an aqueous phase are mixed³³. The organic phase is the homogeneous solution of oil, lipophilic surfactant and water-miscible solvent. The aqueous phase consists of hydrophilic surfactant and water. An experimental study of nanoemulsion process optimization based on the required size distribution was performed in relation with the type of oil, surfactant and the water-miscible solvent¹².

Derivatives: Numerous derivatives of cinnamaldehyde are commercially useful. The example of the first cinnamaldehyde derivative is Dihydrocinnamyl alcohol, which occurs naturally and is produced by double hydrogenation of cinnamaldehyde. It is used to confer the fragrances of hyacinth and lilac^{21, 34}. Second derivative is cinnamyl alcohol similarly occurs naturally and has the odour of lilac (Eurasian shrub of the olive family).

Another derivative is Dihydrocinnamaldehyde, produced by the selective hydrogenation of the alkene subunit. Hydrogenation of cinnamaldehyde usually uses selective catalysts (Pt, Cu, Rh etc) for the synthesis of derivatives such as hydrocinnamaldehyde and cinnamyl alcohol as a sole product³⁵⁻³⁷. Other process hydroformylation of styrene in presence of rhodium complexes as catalyst form is phenyl-propanal³⁷. Phenyl-propanal, that is also categorized as cinnamaldehyde derivative.

Physico-chemical properties: The physical properties of Cinnamaldehyde or trans-cinnamaldehyde with molecular formula C₉H₈O as for chemical formula is C₆H₅CH:CHCHO, Molar mass: 132.16 g/mol, slightly soluble in water about 1.1 g/L at 20 degrees Celsius, density: 1.05 g/mL at

25 degrees Celsius, Melting point: \approx -7.5 degrees Celsius (18 F; 265.6 K), Boiling point: 248 degrees Celsius (478F; 521K). The product of cinnamaldehyde properly stored safely at 0-6 degrees Celsius. Then, the appearance of cinnamaldehyde is clear yellow oil liquid. The strong odor of cinnamon is determined especially in trans-cinnamaldehyde which gives sweet taste.

As for its chemical properties, cinnamaldehyde considered as pH dependent when extraction is done (plant extraction) by ruminal microbial fermentation³⁸. This can be further proved by the fact that the activity of cinnamaldehyde compound at low pH level better efficiency in the stomach of human³⁹. The reactivity of trans-Cinnamaldehyde towards strong oxidizing agents and strong bases is incompatible but it can react with sodium hydroxide. It is also sensitive with prolonged exposure to light and air because of its volatile character⁴⁰. Because of its combustible nature it has to be handled carefully. Trans-cinnamaldehyde as volatile compounds is tested for the influence on microbial count and growth in air by vaporizing with an air washer⁴¹.

Safety precaution: Because of their characteristics, the safety precautions must be taken. Fire involving this chemical can be controlled with a dry chemical, carbon dioxide or Halon extinguisher⁴². Symptoms of exposure to this compound may include inflammation and erosion of gastrointestinal mucosa. Then, the vapour or mist causes irritation of the eyes, mucous membranes and upper respiratory tract⁴³. This chemical may be harmful by inhalation, ingestion or skin absorption. It may cause irritation of the skin, eyes, upper respiratory tract, and mucous membranes. When heated to decomposition it may emit toxic fumes of carbon monoxide and carbon dioxide^{28,44}.

Beneficial effects of cinnamaldehyde:

Flavorant: There is numerous application of cinnamaldehyde that is beneficial to human. The most obvious application for cinnamaldehyde is as a flavouring agent in chewing gum, ice cream, candy, and beverages. It is used at the levels ranging from 9 to 4900 parts per million (ppm) or less than 0.5%⁴². It is also used in some natural and also in perfumes, sweet or fruity scents. So,

almond, apricot, butterscotch, and other aromas may partially employ the compound for their pleasant smells⁷. Then, cinnamaldehyde sometimes used as a food adulterant; powdered beechnut husk aromatized with cinnamaldehyde can be marketed as powdered cinnamon⁴⁵. The cinnamaldehyde flavoring present does not possess any risk to the health of the consumer¹⁷.

Agrichemical: In term of agrochemical application, cinnamaldehyde is used as a fungicide⁴⁶. It is proven effective on over 40 different crops is typically applied to the root systems of plants⁴³. Its low toxicity and well-known properties make it ideal for agriculture⁴⁷. Cinnamaldehyde is an effective insecticide, and its scent is also known to repel animals, such as cats and dogs^{5,48}. It has recently been recognized as a very effective insecticide for mosquito larva with as little as 29 ppm of cinnamaldehyde of it killing half of *Aedes aegypti* mosquito larvae in 24 hours⁵.

Cinnamaldehyde from *C.osmophloeum* possess less strongest antifungal effects in comparison with other sources⁵.

Antimicrobial: Cinnamaldehyde is widely used as an antimicrobial which effectively act^{43,49}. Researchers from the University of Illinois at Chicago have found that cinnamaldehyde/cinnamic aldehyde, when being used, it prevent oral bacterial growth by more than 50%⁵⁰. This compound is very effective against bacteria living at the back of the tongue, reducing anaerobic bacteria populations by about 43%⁵¹. Furthermore, cinnamaldehyde is indicated in anticaries treatments as it exhibits the greatest antimicrobial potency at the concentration of 1.25-2.5 mg/ml as compared to other essential oils⁵⁰. It is reported that the edible films and coating containing antibacterial essential oil active component cinnamaldehyde, can be used to protect raw chicken pieces against bacterial contamination without adversely affecting the sensory preference of the baked wrapped chicken^{52,53}.

In order to protect chicken contamination, trans-cinnamaldehyde is applied as a disinfectant/antimicrobial additive for killing certain bacteria (*C.jejuni* and *S.enteritidis*) within appropriate temperatures (12.5 °C and 25 °C) quite effectively⁵².

Anticancer: Recent research reports⁵⁴ documented the anticancer activity of cinnamaldehyde/cinnamic aldehyde was observed in cell culture and animal models of the disease. Proliferation, invasion, and tumor growth were inhibited in a murine A375 model (rats and mice) of human melanoma (skin cancer), though only at high doses of cinnamaldehyde⁵⁵. However such effects were not achievable on dietary intake. The study of structure-activity analysis to define structural features which is vital to cinnamaldehyde analogues activity of defining molecular drug targets for promising class of potential anticancer agents have been performed. The result reveal the propenal group and as well as the functional group in the 2'-position of cinnamaldehyde structure possesses anti-cancer activity^{16,55}.

Other therapeutics uses: Almost all researchers believe that present and previous investigation of cinnamon oil application come up to the development of new therapeutic agent⁵⁶. As for therapeutic agent, the production of cinnamaldehyde is from the bark of cinnamon tree was steamed to get the oil for their various applications. The proof from the previous article using trans-cinnamaldehyde thosemicarbazone could develop novel of tyrosinase inhibitors and could develop new cosmetics additive⁵⁷. Cinnamaldehyde itself also act as fungicides/insecticides, corrosion inhibitors it also helps relieve congestion. As a good antifungal^{40,58} with the presence of a conjugated double bond, an aldehyde group and a length of CH chain outside the ring influence the properties⁵. Also it controls blood sugar and good for cardiovascular health, glucose metabolism, has anti-inflammatory components⁴⁵. Cinnamaldehyde otherwise called an erosion inhibitor for steel and different ferrous combinations in destructive liquids.

It can be utilized as a part of blend with extra parts, for example, dispersing agents, solvents and different surfactants. The refractive records make it genuinely sheltered and helpful liquid for analyzing gemstone harsh for considerations. The investigation done previously⁵⁹ reveals the cinnamaldehyde safely use as a natural oral agent with the effects of both hypoglycemic and hypolipidemic which lowered the total cholesterol (antidiabetics). The discovery of transient receptor

potential (TRP) agonist cinnamaldehyde and several chemical have understanding of temperature sensation, pre-clinically identified TRP as major novel analgesic targets in inflammatory and neuropathic pain^{60,61}. These are many semi synthetic modifications of cinnamaldehyde being synthesized to increase the antibiotic susceptibility of drug resistant bacteria⁶².

According to the previous research⁶³ summary which demonstrated that an one hour treatment with trans-cinnamaldehyde (CA) could trigger complete or partial reduction in virus growth by the blocking of viral protein synthesis at certain stage of growth cycle *in-vitro*. Otherwise, the suggestion from the previous experimental study that cinnamaldehyde (*C. osmophloeum*) gives advantage to human health, having the capability to be used for medical purposes and to be utilized as anti-bacterial additive in making paper products⁴⁵. The lysozyme based cinnamaldehyde modification leads to the formation of novel preservatives can be useful for dermatic related area¹⁰.

Cinnamaldehyde in food industry: Cinnamaldehyde are essentially utilized as food enhancing and a therapeutic herb. Over the span of studies intended to find its most extreme microbial lethality under food transforming conditions, a gas chromatographic-mass spectrophotometric system was created for the extraction and examination of essential oil components, for example, cinnamaldehyde from commercial cinnamon-containing foods (a few brands of cinnamon breads, oats, treats, puddings, and fruits juices). The cinnamaldehyde substance went as additive in squeezed orange in apple cinnamon cereals and for cinnamon swirl bread^{1,22,64}.

The high temperature soundness of cinnamaldehyde in nourishment handling was discovered when joined with eugenol or cinnamon leaf oil which gets to be steady considerably after 30 min at 200 °C⁷. Other food application of cinnamaldehyde as containing antimicrobial properties of the coated papers go about as additives to be effective, antimicrobial packaging needed to secure two principle rates in the arrival of active agents: low discharge amid its capacity without contact with items and quick discharge amid its utilization as food packaging in close

contact with items or by vacuum-packaged transformed by utilized of antimicrobial film designed⁶. Because of the hydrophilic nature of the coating matrices, high arrival of the antimicrobial agents was normal at high dampness, that is, great conditions for microorganism advancement⁸. An alternate discovering²² of mix cinnamaldehyde with natamycin offered climb to antifungal bioplastic films against basic sustenance waste microorganisms either *in vitro* or in genuine food stuff. As additive, cinnamaldehyde additionally can be more effective while keeping it in refrigerator temperatures of short of 8 degree Celsius to control the development of psychrotropic strains of the food borne pathogen⁶⁵. An alternate way a developing cinnamaldehyde as essential oil into edible films additionally as wrapping gives a novel approach to upgrade the timeframe of realistic usability and safety in food industry^{3, 66, 67}.

Nevertheless, a couple of studies showed that carvacrol is better than cinnamaldehyde in term of antimicrobial activity^{3, 67}, however cinnamaldehyde act towards various microorganisms than carvacrol. The great response as antimicrobial was indicated with the blend of carvacrol and cinnamaldehyde. Furthermore, the antimicrobial under investigation of cinnamaldehyde could be consolidated with vanilla smell, giving both antimicrobial properties and the smell anticipated that will enhanced nature of food product⁴². At that point, to enhance cinnamaldehyde application in food technology the expansion of amino acid can diminish unsuitable smell of cinnamaldehyde once enhanced food appearance itself⁶⁸.

CONCLUSION: In this review article, cinnamaldehyde as a natural molecule has been presented systematically with a scientific prospective. The molecule has been explained from its source chemistry; physicochemical characteristics and with the synthesis of its different analogous with a view point of imposing certain applicability. Further the applications have been narrated with an intention of creating the background on which future research on the material can be fostered.

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