One of the etiologies for aging is oxidative stress, induced by the action of free radicals (1, 2). These entities are also responsible for deterioration of fats. Since active ingredients of most of the natural extracts obtained from seeds (3, 4) and vegetables (5, 6) are hydrophilic, naturally derived lipophilic antioxidants are essentially needed for using in fat-containing products as well as in vivo. Some lipophilic antioxidants, including butylhydroxyanisole, butylhydroxytoluene, tert-butylhydroquinone and propylgallate, are already being utilized. However, these antioxidants are carefully removed from human diet because these compounds are not safe for health. As a result, potent, safe and natural lipophilic antioxidants are required to stabilize food products (7).

Plant seeds are important source of edible oils, which contain plentiful antioxidants. The antioxidants scavenge oxygen radicals and protect important cellular macromolecules including proteins, lipids, DNA and RNA against oxidative stress in seeds. Thus, the oxygen radical scavengers play an important role in seed germination (8). Additionally, human health can be protected from various oxidative stress-induced pathologies such as cancer (9) and Alzheimer’s disease (10) by using edible oils rich in oxygen radical scavengers including canolol (11).

There is no information about natural occurrence of canolol in plants; however, canolol formation is traced on treating canola oil with heat during roasting canola seeds or during processing and extracting seeds. Since canolol contents are significantly higher in roasted canola seeds as compared to that in pre-roasted seeds, thus food value of canola seeds and its oil can be improved by increasing canolol amount through roasting of canola seeds prior to pressing (12).

Canolol is a phenolic compound and a decarboxylated derivative of sinapic acid (Fig. 1) (13). The decarboxylation of sinapic acid reduces its polarity leading to increased lipid solubility of canolol (14). Due to non-polar nature, it is soluble in oils. This property of canolol advocates its role as food protecting agent and readily bioavailable compound. In comparison to hydrophilic antioxidants, high oral bioavailability of canolol could be due to its lipophilic property responsible for high affinity of canolol to the biomembranes (12).

Abstract: Canolol is a decarboxylated derivative of sinapic acid. Due to lipophilic nature, canolol is an excellent orally bioavailable phenol. It mainly occurs in roasted rapeseeds. It is documented in the literature as a potent antioxidant and safe for human health. The mode of antioxidant activity of canolol involves the suppression of various free radicals such as O₂−, ONOO− and "OOH. As evident from the literature, few studies have been carried out to explore the free radical scavenging activity of canolol. Thus, the objective of this review article is to summarize the available literature about free radical scavenging potential of this promising phenol to pave the way for further investigations about biological activities of canolol.

Keywords: edible oil, sinapic acid, phenol, free radical scavenger, antimutagenicity
The chemical formula of canolol is C_{10}H_{12}O_{3}. Its other names include 2,6-dimethoxy-4-vinylphenol (IUPAC name), 4-vinylsyringol, 3,5-dimethoxy-4-hydroxystyrene and 4-vinyl-2,6-dimethoxyphenol (15).

Being a potent, natural antioxidant, there is increased need and demand of canolol in food industry. Thus, natural production of canolol is insufficient. To satisfy this demand, studies for its chemical synthesis has been carried out. In this context, microbial and chemical processes have been utilized to decarboxylate cinnamic acids including sinapic acid, ferulic acid and caffeic acid obtained from plants such as wheat bran (16), barley (17) and sunflower seeds (18, 19).

There are various scientific evidences that canolol is a potent antioxidant and antimutagenic substance (1, 2, 20, 21). Koski et al. reported canolol as a stronger lipidperoxyl radical scavenging agent than other compounds isolated from canola oil (1). Kuwahara et al. have demonstrated that canolol is a good scavenger of ONOO^- (2). Moreover, antimutagenicity of canolol was found comparable to that of α-tocopherol, quercetin and β-carotene in a dose-dependent manner (2, 12).

Amazingly, up to now, quite limited studies have been carried out to explore the free radical scavenging activity of canolol. Thus, the objective of this article is to summarize the available literature about free radical scavenging potential of this phenol to pave the path for further investigations about biological activities of canolol.

**Literature search methodology**

An extensive literature search in English was carried out, using different electronic databases including Medline (1966-2015) and EMBASE (1980-2015). An initial search was conducted using terms “canolol” and “antioxidant” jointly. Then, other terms such as “inflammation”, “cancer” and “molecular targets” were combined with “canolol” and “antioxidant” for an advanced search. The literature search was conducted by evaluating the bibliography of the chosen publications revealing original research to construct a quality review article.

**RESULTS AND DISCUSSION**

**Antioxidant activity**

The production of reactive oxygen species (ROS) and their consumption in human body is an uninterrupted phenomenon in normal physiological conditions (22). The function of maintaining ROS concentration at a specific level in the body is performed by ROS scavengers, called antioxidants, which are capable of capturing surplus ROS (23). The disturbance in the function of endogenous antioxidants or low antioxidants-ROS ratio may lead to aggregation of ROS in body resulting in aging and various pathologies including cancer and Alzheimer’s disease (24-26). To retrieve normal, dynamic equilibrium between antioxidants and ROS in the body, exogenous antioxidants are required to be ingested. The exogenous antioxidants should be safe to human health. Thus, natural antioxidants are enormously being investigated using various sources including plants, which are capable of producing wide range of antioxidants such as polyphenols (27). There are four main classes of polyphenols including phenolic acids, flavonoids, stilbenes, and lignans, which are capable of scavenging ROS in the body, leading to combat aging and various associated pathologies such as cancer (28). The antioxidant property of polyphenols depends on the presence of methoxy- and hydroxy- groups in polyphenolic structure as in case of canolol (29, 30).

![Conversion of sinapic acid to canolol (15)](image-url)
Canolol is a phenol and possesses excellent antioxidant activity. Various mechanisms of antioxidant activity of canolol have been described in the literature as presented below.

The antioxidative comparison of 500 ppm of each, canolol, sinapic acid and α-tocopherol present in soybean oil, revealed that canolol was the most potent antioxidant. To explore antioxidant effect of canolol, these three antioxidants were added to soybean oil, called test oil. For comparison, control oil consisted of only soybean oil, i.e., without these three antioxidants. Both oils were stored for 19 days to permit their oxidation. At 20th day of storage, the degradation rates of linoleic acid and linolenic acid were noted and found significantly lower in test oil compared to control oil. Moreover, there was significant amount of secondary oxidation products (SOP) such as aldehydes in control oil, while test oil contained the undetectable amounts of SOP (31).

In another comparative study, antioxidant activity of canolol, sinapic acid, rapeseed meal and oil extracts was tested utilizing DPPH* radical scavenging approach. From results, it was found that antioxidant activity of rapeseed oil extract was the highest with an inhibition of 65.4% and 93.8% at 0.5 mg/mL and 1 mg/mL, respectively. The DPPH* radical inhibition by canolol was 37.1 and 78.7%, respectively. Higher DPPH* radical inhibition (%) of rapeseed oil extract could be due to the presence of sinapic acid and sinapine, beside canolol (32), revealing synergism in antioxidant effect (33, 34).

Terpinc et al. decarboxylated four hydroxycinnamic acids, i.e., p-coumaric, ferulic, sinapic, and caffeic acid to get 4-vinylphenol, 4-vinylguaiaicol, canolol and 4-vinylcatechol, respectively, to assess the antioxidant property of these derivatives. Through DPPH* radical scavenging method, these decarboxylated compounds were found to have higher antioxidant activity in the emulsion system as compared to their respective hydroxycinnamic acids. However, non-significant difference was observed in the antioxidant activity of canolol and sinapic acid when superoxide radical (O2−) scavenging approach was used. As a result of this test, antioxidant activity of 4-vinylcatechol was maximal, followed by canolol > 4-vinylguaiaicol. 4-Vinylphenol was found the least antioxidant derivative (34). This outcome is also supported by other studies (35-37).

Canolol scavenge the *OOH more quickly than sinapic acid. Utilizing density functional theory, Niwa et al. studied the anti-*OOH activity of canolol in lipid and aqueous systems and noted it more potent in later condition. As compared to other antioxidants, anti-*OOH activity was found in following decreasing order: canolol > carotenones > allicin > melatonin. Due to lower reactivity of peroxyl radicals than that of other ROS, the authors declare canolol to be an excellent antioxidant, because anti-*OOH reactivity of canolol toward *OOH radicals occurs approximately absolutely by H-atom shift from the phenolic part in canolol (15, 38).

In another study, canolol and its precursor, sinapic acid, were subjected to low density lipoprotein system. Then, two concentrations, 10 µM and 25 µM, of both, sinapic acid and decarboxylated sinapic acid were used to study their antioxidant property. Canolol (7.5%) was found less active than sinapic acid (28%) at a concentration of 10 µM, but surprisingly, the activity of canolol (95.3%) was higher than that of sinapic acid (97.1%) at a concentration of 25 µM (32). It elaborates dose-dependent antioxidant property of canolol.

The viability of human retinal pigment epithelial (ARPE-19) cells can be maintained against oxidative stress by using canolol, which is effective for limiting intracellular level of ROS. Previously, the investigators induced oxidative stress in ARPE-19 cells by using tert-butyl hydroxide (t-BH) and then administered 200 µM of canolol, which reduced ROS concentration to a level as in normal physiological conditions. Moreover, antioxidant effect of canolol was stronger than reference antioxidant, N-acetylcysteine. The antioxidant activity of canolol was dose-dependent. In addition, ARPE-19 cells pre-treated with canolol remained safe on treating with t-BH showing protective effect of canolol. The authors attributed this protective effect of canolol to activation of ERK (extracellular signal-regulated kinase)-mediated pathway that alternatively, activate antioxidant enzymes such as heme oxygenase, catalase, and glutathione S-transferase-Pi (39).

An in vivo study on broiler chickens also confirmed the antioxidant property of canolol. In this animal model, corticosterone was used to induce oxidative stress that suppressed the chicken growth. On using canolol, there was reduction in the growth suppression. The authors attributed antioxidant feature of canolol to its capability to reduce lipid peroxidation. Another reported possible mode of action of canolol was its potential to maintain elevated concentration of α-tocopherol in liver and muscle tissues under normal or oxidative stress state (40).

**Bactericidal and antimutagenic activity**

In contrast to nitric oxide (NO), ONOO−, a metabolite of NO, possesses bactericidal and oxidative characteristics (41). Its oxidative feature is
responsible for mammalian cells apoptosis. Such mutagenicity was successfully cured by Kuwahara et al. by using > 8 µM of canolol in a dose-dependent manner. The anti-ONOO\(^-\) activity of canolol was proposed as possible mode of its antimutagenic property. The DNA protective effect of canolol was greater than that of \(\alpha\)-tocopherol, an antioxidant. On the other hand, bactericidal activity of canolol also depends on its anti-ONOO\(^-\) activity. To study the antimicrobial effect of canolol, the constant flux method was employed using Salmonella typhimurium culture. From the results, canolol was found to be bactericidal in a concentration as low as 0.1 mM. Conclusively, ONOO\(^-\) induced oxidation is possible to be inhibited by canolol. It leads to prevention of apoptosis of bacterial and mammalian cells (2).

Anti-inflammatory and anticancer activity

In an \textit{in vivo} study, the protective action of canolol against inflammatory bowel disease and colitis related carcinogenesis through suppression of inflammatory cytokines and oxidation stress was detected (42). Colon cancer generally arises from oxidative stress induced-inflammatory bowel disease and colitis. Fang et al. induced colitis in mouse by oral administration of 2% dextran sulfate sodium (DSS) marked by the increased level of inflammatory cytokines including interleukin-12 and tumor necrosis factor-\(\alpha\). Then, the canolol rich diet was administered to the diseased mouse resulting in the suppression of pathogenesis accompanied with significant reduction in the level of inflammatory cytokines as compared to that of pathological state. In the same experiment, they administered canolol to mice with azoxymethane/DSS-induced colon cancer and noted reduction of cancer growth by 40% in comparison to that of control mice (no treatment with canolol). In addition, there was significant reduction in the level of inflammatory cytokines as compared to that of pathological condition. Mouse treated with canolol did not show any symptoms of toxicity. It can be concluded that canolol is an effective chemopreventive drug against inflammation and cancer (42). Additionally, Sun et al. documented the canolol induced-suppression of various inflammatory cytokines including interleukin-1\(\beta\), tumor necrosis factor-\(\alpha\), interferon-\(\gamma\) and cyclooxygenase-2 suggesting anti-inflammatory action of canolol (43).

Gastric cancer is second major cause of cancer-associated mortality worldwide. Canolol represents an interesting chemical compound for consideration as a preservative in foods, cosmetics, and the pharmaceutical industry. In the future, anti-hyperglycemic, and neuroprotective studies of canolol may also be conducted. Pharmacokinetic studies of canolol should also be carried out to explain relationship between the plasma concentrations of canolol, in therapeutic dose and the therapeutic benefits.

REFERENCES


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