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REVIEW

Recent Updates on Anti-Inflammatory and Antimicrobial Effects of Furan Natural Derivatives

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Abstract: The furan nucleus is found in a large number of biologically active materials. In recent years, many natural furan derivatives were isolated and their biological effects were investigated. In this review, we focused on the anti-inflammatory and antimicrobial effects of some natural furans and discussed their effects on the immune system. Our investigation revealed that furan natural derivatives have effective antioxidant activities and exert regulatory effects on various cellular activities by modifying some signaling pathways such as MAPK (mitogen-activated Protein Kinase) and PPAR-ɣ (peroxisome proliferator-activated receptor gamma). The antimicrobial activity of these natural compounds was performed through selective inhibition of microbial growth and modification of enzymes. Further studies are needed for isolation and detection of different furan derivatives from natural compounds and investigation of their precise mechanisms for revealing health beneficial effects of these compounds.

Keywords: anti-inflammatory, antimicrobial, furans, benzofurans, furan natural derivatives

Introduction

Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen. The class of compounds containing such rings is also referred to as furans. Furan is a colorless, flammable, highly volatile liquid with a boiling point close to room temperature.[1,2] Furan derivative is an imperative class of heterocyclic compound that has important biological properties.[3–5] Furan is rapidly and extensively absorbed from the intestine and the lung. It can pass through biological membranes, and enter various organs. Compounds comprising the furan or tetrahydrofuran ring are biologically active and are existent in a number of pharmaceutical products. Furfurylamine is an intermediate in the diuretic, furosemide. 5-(Di methyl amine methyl) furfuryl alcohol is an intermediate in the preparation of ranitidine, which is used for treating peptic ulcers. 2-Acetylfuran, prepared from acetic anhydride and furan is an intermediate in the synthesis of cefuroxime, a penicillin derivative. 2-Furoic acid is prepared by the oxidation of furfural. Both furoic acid and furoyl chloride are used as pharmaceutical intermediates. The compounds and its derivatives are naturally occurring in many foods.[6,7] In recent years, many furan derivatives are isolated from natural compounds such as plants,[8] fruits,[9] oils[10] and marine foods.[11] Numerous investigations showed that these furan derivatives possess beneficial effects on human health.[12,13] Some previous investigations based on cumulative data drawn from animal models suggested that furans are mainly carcinogenic agents and possibly can be carcinogenic to humans.[14] The furan ring system is the basic skeleton of numerous

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compounds possessing cardiovascular activities.[15] These compounds are widely employed as antibacterial, antiviral, anti-inflammatory, anti-fungal, anti-tumor, anti-hyperglycemic, analgesic, anti-convulsant, etc.[16–19] More recently, an increasing body of evidence indicated that furans may possess some desirable immune-regulatory effects. Several Furans natural derivatives have been introduced with favorable biological functions including antioxidant activity, anti-proliferative and antiviral activity.[7,20] Moreover, furan, benzofurans, furan fatty acids, agarofurans and furanocoumarins derivatives constitute a major group of furan natural derivatives that exhibited extensive pharmacological activities such as anti-inflammatory and antimicrobial effects (Figure 1). Despite these findings, there are so many doubts about the actual therapeutic potential of these compounds due to lack of knowledge about their complex effects on all features of human health. Therefore, in this review, we focused on the mechanisms of anti-inflammatory and antimicrobial activities of some natural furan derivatives (Table 1).

Methods

A literature search of the PubMed and Embase databases was conducted for the terms "natural furans", "furan natural derivatives", "anti-inflammatory" and "antimicrobial". Searches were limited to English-language articles published prior to or on January 29, 2019. Results of any relevant articles were manually identified by the authors for review and duplicate articles were excluded.

Natural Benzofurans

Benzofuran is a colorless liquid with an aromatic odor, boiling point (101.3 kPa) 171.4°C, density (20°C) 1.0948 g/cm3, melting point (−28.9°C) and can be synthesized by dehydrogenating and cyclization of 2-ethylphenol.[19] It is a heterocyclic organic compound with two benzene rings fused to a central furan ring (Figure 1B). Natural derivatives of benzofuran can be produced in some trees[21] and plants.[20]

Anti-Inflammatory Properties of Natural Benzofurans

Some investigations showed that benzofuran natural derivatives can affect immune responses in some cell lines. In this way, Jih-Jung Chen et al isolated a new dibenzofuran, lucidafuran and some known compounds from the stems of a small endemic deciduous tree and investigated their anti-inflammatory effects. The anti-inflammatory effects of the isolated compounds were evaluated on fMet-Leu-Phe (fMLP)-induced O_2 generation by human neutrophils. They indicated that lucidafuran and another dibenzofuran derivative eriobofuran inhibited O_2 generation of human neutrophil.[22]

Another study by Chu-Hung Lin et al confirmed the inhibitory effects of some dibenzofuran natural derivatives on human O_2 generation. Four dibenzofuran compounds from roots of *Rhaphiolepis indica*, including 2-hydroxy-3,4,6-trimethoxydibenzofuran, 2-hydroxy-3,4,9-trimethoxy-dibenzofuran, 2-hydroxy-3,4,6,9-tetramethoxydibenzofuran, and 1,2-methylenedioxy-3,4,6-trimethoxydibenzofuran were shown to efficiently suppress O_2 production by human neutrophils.[23] Natural derivatives of benzofuran such as 2-arylbenzo [b] furan, egonol, XH-14, and ailanthoidol were studied by Hwang et al for possible anti-inflammatory effects in lipopolysaccharide (LPS)-stimulated RAW 264–7 macrophages. It was found that these compounds significantly inhibited the production of inflammatory mediators, nitric oxide, without showing any significant cytotoxicity. Furthermore, ailanthoidol was the most anti-inflammatory compound with a unique possibility to inhibit nitric oxide (NO) production at 10 μM.[24]

Furthermore, Park et al investigated the anti-inflammatory effects of XH-14, isolated from *Salvia miltiorrhiza*, and revealed that this compound can inhibit LPS-induced NO production in a dose-dependent manner most probably via a reduction in iNOS protein expression.[25] They also noticed that PGE2 was decreased after the exposure to XH-14. Previous studies showed that pro-inflammatory mediators such as mRNA expression of iNOS, COX-2, IL-1β, and IL-6 were significantly decreased by exposure to 5 and 20 μM concentrations of XH-14. This has been widely adopted that pro-inflammatory prostanoids such as PGE2 play a key role in guiding and governing various aspects of the inflammatory responses. This property has been linked to activities of inducible COX-2. Therefore, the production of PGE2 is often taken as an indicator of COX-2 activity and its inhibition as an index of the ability of COX-2 selective inhibitors.[26–28] Many natural neolignans have displayed significant potential as a novel anti-inflammatory compound.[29] XH-14, which is also known as Danshen can bind the A1 adenosine receptor with relatively high affinity and inhibit adipocyte differentiation and induction of the adipokines in adipocytes.[30] XH-14 also might be attributed to its inhibiting effect on PGE2 production through blocking COX-2 gene expression as well as the activity of COX-2.[25] Furthermore, synthesized derivatives tend to have significant anti-inflammatory activity and

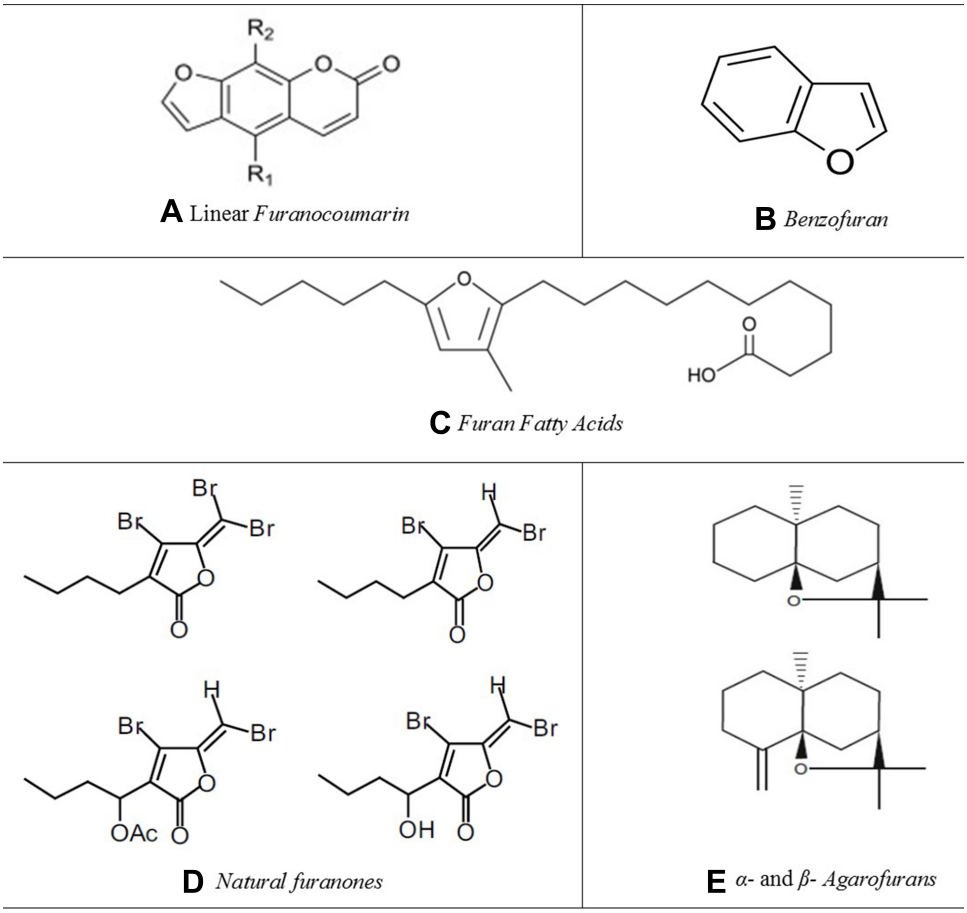

Figure 1 Structure of Furan natural derivatives. Panels A-E depicted different form of furan natural derivatives as; linear Furanocoumarin (**A**), Benzofuran (**B**), Furan fatty acids (**C**), natural Furanones (**D**) and α- and β- Agarofurans (**E**).

shall prove as structural templates in the design and development of new anti-inflammatory drugs.[31]

Moreover, benzofuran can exert regulatory effects on various cellular activities, potentially by modifying signaling pathways such as MAPK and PPAR-ɣ.[32] As well, Park et al studied MAPKs pathways by evaluating the phosphorylation of JNK, p38, and ERK. The phosphorylation of these proteins was inhibited after treatment with different doses of XH-14 through stimulation with LPS.[25] Induction of PPAR-ɣ and C/EBPα as transcription factors that regulate adipocyte marker genes was inhibited by XH-14 derivative and suggested as therapeutic applications against obesity-related metabolic and inflammatory diseases.[30]

In general, compounds with benzofuran skeleton, such as ailanthoidol, XH-14, and egonol are natural products that are known as characteristic members of the benzofuran lignan family. Benzofuran lignans mostly contain a 2-phenyl-7-methoxy-benzofuran skeleton that may possess a substantial role in anti-inflammatory properties of natural benzofurans.[33] The exact mechanism by which benzofuran exhibits anti-inflammatory actions is not clear yet. It seems that it can inhibit the production of PGE2 and at the same time can decrease lipoxygenase activity.[29]

Another anti-inflammatory property of benzofuran is the ability to inhibit NO production as a free radical that is involved in various inflammatory responses.[25,34] Therefore, it has been proposed that NO scavenging by benzofuran plays an important role in the regulation of inflammatory pathways.

Antimicrobial Properties of Natural Benzofurans

Anti-fungal activity of natural dibenzofurans is responsible for another possible effect of these compounds on the human immune system. In an investigation that was conducted by Qu et al they isolated dibenzofuran bis (bibenzyl) from the liverwort *Estrella angusta*. The anti-fungal activity was

Table 1 Suggested Pathways for Anti-Inflammatory Activity of Some Natural Furans

Furan Derivatives	Source	Effect	Ref.
Benzofurans	Some trees (mulberry tree) and plants	• Suppress O_2 production by neutrophils • Inhibit nitric oxide (NO) production • Modify MAPK pathways and PPAR-ɣ gene expression	[21,25,35]
Furan fatty acids	Fishes, Grasses, Wheat, Potato, Soya bean oils	• Hydroxyl radical scavengers • Antioxidant activity • Decrease mitochondrial dysfunction	[42,43,45]
Furanocoumarin	Fruits (lemon peel, grapefruit), Vegetables (parsleys, celery)	• Protect against lipid peroxidation • Inhibition of cyclooxygenase and lipoxygenase • Reinforcing enzymatic and non-enzymatic antioxidants	[46,53,56,59]
Agarofurans	Some fruits and seeds	• Chelation of the transition metal ions • Down-regulation of NF-κB gene expression	[73,80,81]
Furanones	Some sea organisms, pineapple, mushroom	• Inhibit activation of NF-κB and MAPKs pathways • Superoxide anion scavengers • Inhibit peroxidation	[94, 96, 97]

investigated by evaluating minimal inhibitory quantity (MIQ) and minimal inhibitory concentration (MIC) of these compounds on *Candida albicans* and results showed that dibenzofuran bis (bibenzyl) might be an anti-fungal compound with MIC values ranging from (16 µg/mL) to (512 µg/mL).[35] It has been stated that benzofurans, accompanied by anti-microbial effects, can inhibit the fungal activity and previous in-vivo studies indicated anti-fungal activity of natural dibenzofuran compounds such as *Entomosporium eriobotryae*,[36] *Venturia inaequalis*[37] and *Chondrostereum purpureum*[38] in some hosts pathogenic fungus. This finding may offer new insights about potential therapies from a fungal disease, but their effects on human pathogens need more investigations.

Natural Furan Fatty Acids

Furan fatty acids (F-acids) are a class of heterocyclic fatty acids which have a furan moiety in the central part of the molecule (Figure 1C). F-acids with methyl or dimethyl substituents on the furan ring are known as valuable minor fatty acids in foods and have been found in the lipids of various fishes,[39] plants such as grasses, wheat, potatoes[8] and soya bean oils.[40,41]

Anti-Inflammatory Properties of Natural Furan Fatty Acids

Numerous studies have confirmed the anti-inflammatory effects of F-acids, which isolated from the planet and animal sources. In this way, Wakimoto et al showed the anti-inflammatory effects of F-acids, isolated from the green-lipped mussel, on an arthritis-induced model of rats. This in-vivo study indicated that swelling of the paw in F-acids groups was lower than in the control, suggesting that anti-inflammatory effects of these compounds are more potent than of or that of eicosapentaenoic acid.[42] Naturally occurring F-acids are potent hydroxyl radical scavengers and serve as an antioxidant in many biological systems. Competition of F-acids with DMPO (5,5-Dimethyl-1-pyrroline N-oxide) for hydroxyl radical ($HO^{\bullet}$) scavenging activity resulted in a reduction of DMPO-OH adduct signal and F-acids were found to react rapidly with $HO^{\bullet}$ at approximately a diffusion-controlled rate.[43] Besides, Okada and colleagues examined hydroperoxide-decomposer and a chain-breaking antioxidant activity of F-acids and concluded that antioxidant properties of these compounds could not be related to the decomposition of hydroperoxides. For investigating a chain-breaking antioxidant activity, they evaluated the reduction of DPPH (2, 2-diphenyl-1-picrylhydrazyl) and reaction of F-acids toward the peroxyl radicals generated from a radical initiator, AAPH (2, 2′-Azobis (2-amidinopropane) dihydrochloride). Generation of peroxyl radical from linoleic acid oxidation was decreased by scavenging activity of F-acids.[44]

It seems that the extraction of F-acids from natural resources is one of the most important steps of these studies. Factors such as instability and exposure time of

fatty acids in the environment may decompose these compounds and influence the results of such studies. Therefore, the selection of the exact method for extraction of F-acids is a determining factor for the evaluation of the anti-inflammatory effects of these compounds. As well, Teixeira et al treated rat brain astroglioma cells with F-acids and concurrently with hydrogen peroxide as oxidative stress inducer. They showed that cell leakage or mitochondrial dysfunction of astroglioma cells was decreased after the exposure with F-acids and radical scavenging activity of these compounds sufficiently protected astroglioma cells from oxidative stress-induced by the hydrogen peroxide. It is proposed that oxidative stress is rescued by F-acids species scavenging radicals elicited by lipid peroxidation within the cell membrane. Oxidative processes outside the cell membrane, such as protein carbonylation, are not affected by the F-acids species.[45]

It appears that anti-inflammatory properties of natural furan fatty acids are closely linked to the high antioxidant properties of these compounds. It is known that F-acid's antioxidant activity is mainly due to the electron transferability of the furan ring to peroxyl radical or addition of peroxyl radical to the ring.[44] However, our review indicates that there are still many gaps and inconsistencies in revealing underlying mechanisms involved in the anti-inflammatory properties of these compounds which warrants further investigations.

Antimicrobial activity of furan fatty acid, 7, 10-epoxyoctadeca-7, 9-dienoic acid against methicillin-resistant Staphylococcus aureus (MRSA) has been reported in previous studies. Dasagrandhi et al demonstrated that anti-staphylococcal activity of 7.10-EODA and its consequences on cell physiology in disc diffusion and conclude that the utilization of furan fatty acids as novel anti-MRSA agents.[46] A similar conclusion was reached by Knechtle et al, who demonstrated that the furan fatty acid is an inhibitor of Trichophyton infection.[47]

Natural Furanocoumarins

Furanocoumarins (FCs), characterized by a furan ring fused with coumarin, are known as secondary organic chemical components.[48] Furanocoumarins (Figure 1A) are divided into two subgroups, including linear furanocoumarins (Psoralen, Imperatorin, Isooxypeucedanin, Pabulenol, etc.)[49] and angular furanocoumarins (Angelicin, Isobergapten, Sphondin, Pimpinellin, etc.).[50] These chemicals are widely distributed in fruits (lemon peel 75 μg g-1),[48] vegetables (parsnip 26.2 μg g-1, parsleys 1.4 μg g-1),[51] celery (49.8 μg g-1)[52] (DI, grapefruit juices and many other plants.[53]

Anti-Inflammatory Properties of Natural Furanocoumarins

The anti-inflammatory effects of these compounds were investigated through different in-vivo and in-vitro studies. Amponsah et al investigated the anti-inflammatory and antioxidant activity of furanocoumarins from the stem bark of *Moraceae*. Carrageenan-induced foot edema, a model of inflammation in the chick, was used to investigate the anti-inflammatory effects of these compounds. Two furanocoumarins, bergapten, and oxypeucedanin hydrate exhibited significant anti-inflammatory activities in a dose-dependent manner with ED50 values of 01.6±0.003 mg/kg and 126.4 ±0.011 mg/kg, respectively.[54] This finding was consistent with a previous study which claimed that bergapten, isolated from *Angelica pubescens*, has both anti-inflammatory and analgesic activities in mice.[55,56] Interestingly, the inhibitory effect of furanocoumarins from *Kaffir lime* on the production of iNOS and COX-2 was reported in previous studies.[57]

Several natural compounds with a coumarinic moiety have been reported to elicit many biological activities.[48] Coumarin Ring consists of fused benzene and α-pyrone rings. These structures enable the compounds to be carried out by proteins through microvessels into tissue spaces.[18] This may explain how these compounds can inhibit tissue swelling and edema as reported by Fylaktakidou et al. These effects might be explained by the findings due to lysosomal enzymes by macrophage activation and proteolysis.[58] In addition, other studies indicated that the anti-inflammatory effects of many natural compounds such as luteolin, and anthocyanidin are due to a hydroxyl group presented in their structure.[59] Also, the antioxidant activity of furanocoumarins was examined by examining the DPPH scavenging activity of these compounds. There was a high antioxidant activity of oxypeucedanin hydrate as compared to bergapten which was attributed to the presence of hydroxyl groups on the 5-oxyprenyl side chain.[54] In line with these findings, Lan Piao et al concluded that structural specificity might be the main factor in demonstrating the antioxidative activity of furanocoumarins. Hydroxyl group's position might result in different antioxidative activities of individual coumarin components on AAPH-induced cell damage. Further investigations showed that other furanocoumarins such as 9-hydroxy-4-methoxypsoralen and 4-Hydroxy-9-(3-methyl-2-buten-1-yl) −7H-furo [3, 2-g] [1] benzopyran-7-one are potent antioxidants.[60] However, more studies are needed to reveal their exact mechanisms.

Moreover, it is shown that linear furanocoumarins possess a protective ability in rat myocardium against lipid peroxidation. A particular furanocoumarin named as marmesinin significantly reduced the level of lipid peroxides in both the heart and serum in rats, which could be due to the fact that marmesinin blocks the formation of lipid peroxides from fatty acids. The reduction of lipid peroxides by marmesinin is most likely mediated via inhibition of cyclooxygenase and lipoxygenase activity on arachidonic acid.[61]

Inhibition of prostaglandin E2 (PGE2) syntheses by furanocoumarins is another clue for the anti-inflammatory property of these compounds. Also, Seung Ban et al investigated the effect of five furanocoumarins, isolated from *Angelica dahurica*, on lipopolysaccharide (LPS)-induced PGE2 production in rat peritoneal macrophages. They suggested that furanocoumarins suppressed PGE2 production via inhibition of COX-2 and mPEGS expression that this suppression might be the same as that for the inhibition of iNOS expression by similar transcription factors. Phospholipase A2 that catalyzes the hydrolysis of the Sn-2 position of membrane glycerophospholipids to liberate arachidonic acid (AA) might have no role in suppression of PGE2 production.[62] In addition, an in-vivo study by Jhong Huang et al demonstrated that imperatorin has an inhibitory effect on the serum PGE2 level of mice. They revealed that imperatorin decreased Carr-induced iNOS and COX-2 expressions in paw edema.[63]

Activities of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and Glutathione peroxidase (GPx) might be a feature of the anti-inflammatory mechanism of furanocoumarins as the activity of these enzymes increased significantly after treating with furanocoumarins. The inhibition of iNOS and COX-2 expressions has been proposed as a potential therapy for different inflammatory disorders. Large amounts of iNOS could lead to inflammation. In many inflammatory diseases, excessive iNOS expression has been observed.[64] So, it would be interesting to improve potent and selective inhibitors of iNOS and COX-2 expressions for possible therapeutic use (Figure 2).

Antimicrobial Properties of Natural Furanocoumarins

Furanocoumarins are a kind of organic compounds produced by plants which have diverse effects on many organisms.[65] Furanocoumarins, isolated from the *Heracleum maximum* root extract were identified as anti-mycobacterial compounds. Besides, 6-isopentenyloxyisobergapten was more active than other furanocoumarins by MICs of (167μM) and IC50s of (27 μM) against *Mycobacterium tuberculosis* that it may be related to isoprenyl group attached to this compound. The antimicrobial activity of 8-geranyloxy psoralen, a furanocoumarin isolated from *Prangos uloptera* roots, was examined against *Staphylococcus epidermidis, Bacillus subtilis, Escherichia coli, Candida glabrata, Candida krusei* and *Candida kefyr*. As well, 8-geranyloxy psoralen showed the most antibacterial activity against *Staphylococcus epidermidis* by MICs of (100 mgmL-1) and anti-fungal effects against *Candida krusei* and *Candida kefyr*, with MICs of (300 and 100 mgmL-1), respectively.[66] Razavi et al indicated that furanocoumarins are more effective on gram-positive bacteria.[67] Moreover, furocoumarins inhibited auto-inducer (AI) signaling and biofilm formation in bacteria. As well, Girennavar et al isolated furocoumarins from grapefruit and investigated the effect of these natural compounds on different bacterial strains. The results indicated that furocoumarins of grapefruit juice were potent inhibitors of both N-acylhomoserine lactone (AI-1) and molecule, autoinducer-2 (AI-2) activities, while interfere with bacterial growth was not observed.[68] Despite many studies exhibited the antimicrobial activity of natural furanocoumarins, recognition of the precise mechanism of these compounds against microbial activity needs more investigations (Figure 3).[69–71]

Natural Agarofurans

Agarofurans (Figure 1E) are other furan derivatives that can be isolated from plants,[72] trees,[73] fruits[74] and seeds.[75] Many biological activities of these compounds are investigated and revealed new insight into the study about their effect on human health regarding their cytotoxic,[76] immunosuppressive,[77] antitumor activities,[78] and possible anti-HIV properties.[79]

Anti-Inflammatory Properties of Natural Agarofurans

Arciniegas et al isolated two esterified polyhydroxyagarofurans of *Mortonia greggii* gray and investigated their anti-inflammatory activity in carrageenan and 12-O-tetradecanoylphorbol-13-acetate induced models of inflammation. They indicated that agarofuran derivative, 6-acetoxy-1, 9-dibenzoyloxy-4-hydroxydihydro-β-agarofuran, inhibited carrageenan-induced paw

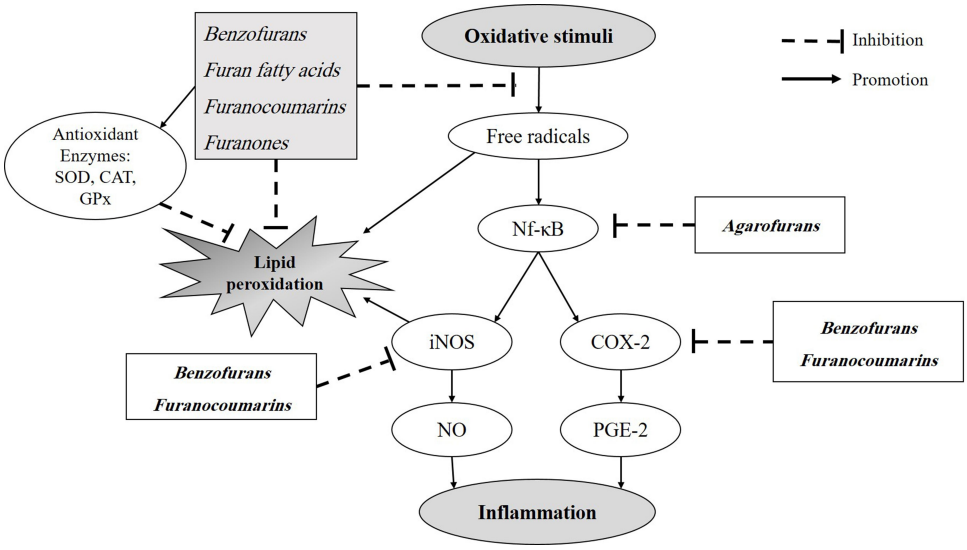

Figure 2 Possible pathways that suggested for anti-inflammatory effects of furan natural derivatives.

edema and 1, 2, 6, 14-tetraacetoxy-9- benzoyloxydihydro-β-agarofuran inhibited TPA-induced ear edema in rats. Also, NO production in LPS (lipopolysaccharide)-activated macrophages were suppressed by these two agarofuran derivatives and this activity could be related to effects on iNOS synthesis.[74] Many studies have indicated that the activity of anti-inflammatory compounds could be eliminated by the deletion of the hydroxyl group.[80] Thus, it seems that the hydroxyl group in various agarofurans may induce anti-inflammatory properties. Zi Jin et al investigated the anti-inflammatory effect of β-agarofuran isolated from *Celastrus orbiculatus* and determined that these compounds inhibited LPS-induced NF-κB activation and decreased NO production in murine macrophage RAW264.7 cells.[81] Using agarofuran compounds as anti-inflammatory agents, which selectively downregulate pro-inflammatory genes, maybe another aspect of their activity. Carroll et al isolated agarofurans from seeds of *Celastrus subspicata* and investigated the expression of pro-inflammatory genes associated with the glucocorticoid receptor-ligand complex. They suggested that these compounds can downregulate pro-inflammatory genes and also can be mildly cytotoxic.[82] Taken all together, anti-inflammatory properties of agarofurans are dependent on two factors; 1) the metal-chelating potential, which is strongly dependent on the arrangement of the hydroxyl group around the molecule and 2) the presence of hydrogen-/electron-donating substituents which reduce free radicals.

Natural Furanones

Furanone is a heterocyclic organic compound that classified as an unsaturated lactone.[83] Natural halogenated furanones (Figure 1D) isolated from sea organisms[84] and also other natural furanone derivative compounds found in a number of fruits.[85] 2,5-Dimethyl-4-hydroxy-3-[2H] furanone (DMHF) or furanone derivatives or furanone compounds was the first furanone that isolated and identified in pineapple.[86] The biological activity of these compounds has recently been identified and medicinal chemistry synthesized their derivatives as effective compounds.[87]

Anti-Inflammatory Properties of Natural Furanones

Furanones are potent superoxide anion scavengers and lipid peroxidation inhibitors.[87] The antioxidative activity of one of the furanone derivative, 4-hydroxy-3 (2H)-furanones, was investigated on the onset of cataract in spontaneous cataract rats. This compound that has been isolated from natural sources such as pineapple and strawberry inhibited spontaneous cataract formation. Reduction of ferric ion and lipid peroxidation were measured for investigating the antioxidative activity of furanone derivatives, and the results showed that although the antioxidative activity of these furanone derivatives was significantly lower than vitamin C, the inhibition of cataract formation was related to the suppression of lipid peroxide.[88] Moreover, Henning et al evaluated the antioxidant activity of 2, 5-Dimethyl-4-hydroxy-3-[2H] furanone (DMHF) in-vitro to determine

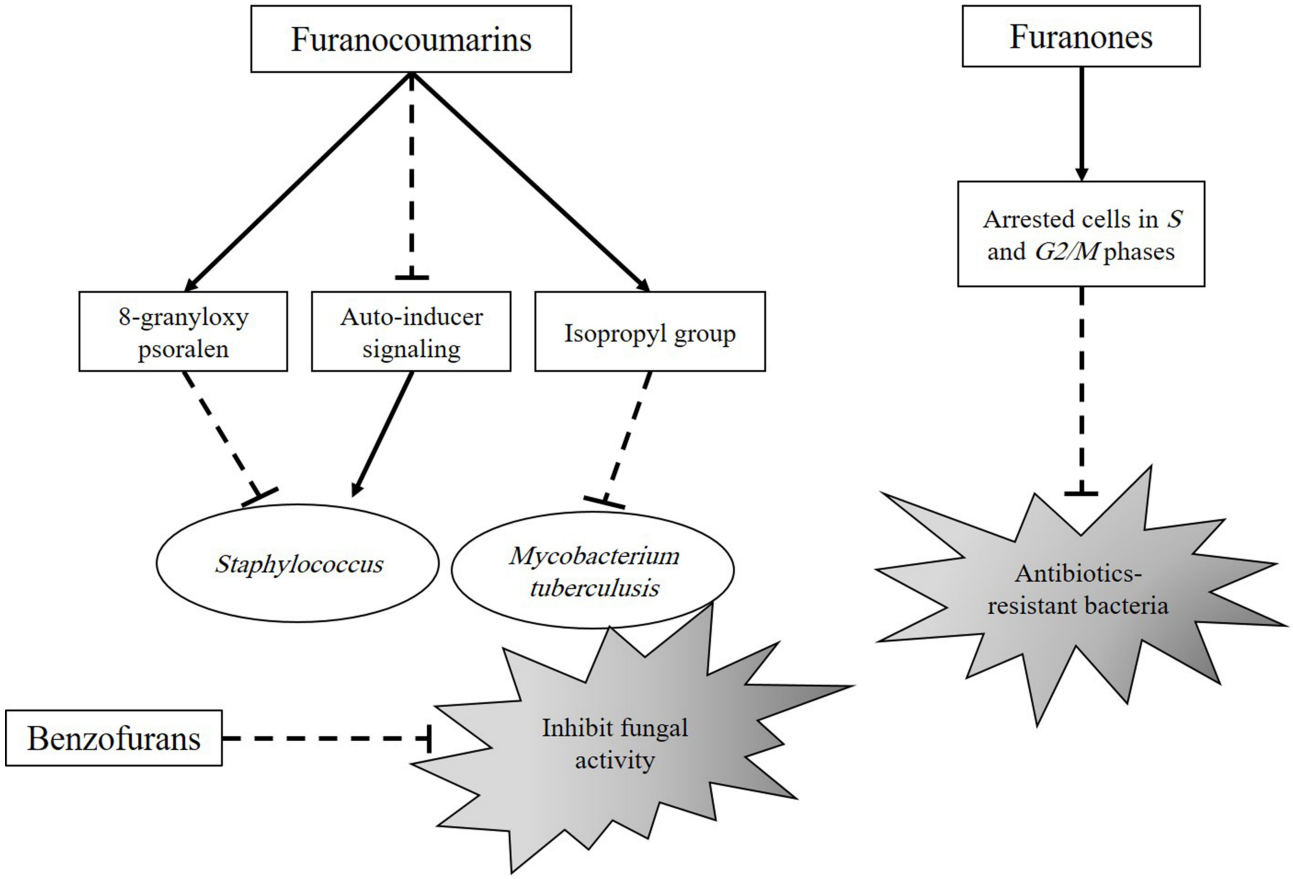

Figure 3 Possible pathways that suggested for antimicrobial effects of furan natural derivatives.

its potential contribution to the health benefits of strawberries. They suggested that DMHF may contribute considerably to the total antioxidant activity of strawberries.[89] Another study indicated 4-Hydroxy-2 (or 5) -ethyl-5 (or 2) -methyl-3 (2H)-furanone can protect the iron in human erythrocyte membranes from ion-induced oxidative modification and can be considered as a potential antioxidant agent.[90] In addition, some furanones which extracted by acetone from the mushroom showed effective antioxidant and anti-inflammatory activities.[91] Oxidative stress has been investigated during inflammation and elevated levels of malonaldehyde, as a lipid peroxidation marker, were found in a remote localized inflammation.[92,93] Consequently, scavengers of superoxide and hydroxyl radicals were effective as anti-inflammatory agents.[94] The results indicate that several states of reduced oxygen and lipid peroxides are involved in the inflammatory response, and natural Furanones are potent superoxide anion scavengers which in turn reduce chronic inflammation. Besides phenol moieties that exist in all families of plants are well known for their antioxidant properties. Numerous investigations have already shown that these natural compounds have diverse effects on human health, including ameliorating of oxidative stress and subsequent diseases. Investigations of mechanisms have revealed that phenol moieties may scavenge free radicals and ROS such as superoxide anion and suppress the production of TNF-α, as a pro-inflammatory cytokine, LOXs, iNOS, chemokines, and other inflammatory molecules (Figure 2). Also, these molecules can inhibit NF-κB and MAPKs pathways.[24,95] Moreover, two aromatic rings on the furanone skeleton enhance the lipophilicity of these compounds which enhance its antioxidative and anti-inflammatory effects. Taken all together, it is expected that the presence of enol and phenol moieties in furanones could induce free radical scavenger activity and related effects.[87] Using the total extract of foods to evaluate the antioxidative or anti-inflammatory effects is the most important weakness of the studies, because in this situation, the identification of the precise mechanism effect of a component may be impossible due to the synergistic or antagonistic effects of different components in combination with together.

Therefore, it may be necessary to separate each compound from the total extract and examine those compounds separately.

Antimicrobial Properties of Natural Furanones

In an investigation by Sung et al, the antimicrobial effects of DMHF on various human pathogens, including antibiotic-resistant bacteria were confirmed. This compound showed the antibacterial activity against gram-positive and gram-negative bacterial strains which performed through an energy-dependent manner and arrested the cell cycle at the *S* and *G2*/*M* phase.[96] In another study, Ren et al studied the antimicrobial activity of halogenated furanones, one of the furanones derivative that isolated from the marine red algae *Delisea pulchra*, revealed that these compounds inhibited swarming and biofilm formation of *E. coli* without affecting its growth.[97] Furanone also inhibited quorum sensing mediated behaviors by interfering with various N-Acylhomoserine lactone (AHL) signal compounds of different acyl chain lengths. This result indicated that furanone can be an effective quorum-sensing (QS) inhibiting against many different bacterial genera that produce different types of AHL signal molecules.[98] These compounds suppressed swarming motility by targeting the quorum-sensing receptor. Also, furanones compete with N-butanoyl-L-homoserine lactone (BHL) in their binding position to the receptor, disrupt the autoinducer-2 (AI-2) biosynthetic pathway[99] and modify and inactivate S-ribosylhomocysteinelyase (LuxS), the enzyme which produces AI-2.[100] A similar conclusion was reached by Chepkiruia et al who show that moderate antimicrobial activity against various test organisms of new furan.[101]

Knowledge Gaps and Future Directions

To illuminate uncharted areas of the effects of furan derivatives on inflammation and oxidative stress biomarkers, future investigation should focus on the effect of furan derivatives as potent inhibitory activities against lipoxygenases (LOXs) which plays crucial roles in inflammatory diseases. So, it is proposed that the effects of furan derivatives on other activities involved in LOXs pathways will be examined in future studies.

Conclusion

The study of furan natural derivatives is tough and complex due to the heterogeneity of the different molecular structures and the inadequacy of investigation about related mechanisms. The reviewed furan moiety has shown a wide spectrum of biological activities. Various substituted furan is having significant antimicrobial and anti-inflammatory activity. In recent years, many furan derivatives are isolated from a variety of natural organisms such as plants, fruits, vegetables, marine organisms and oils, and their biological effects are intensively investigated.[1,7] Many studies have revealed that furan natural derivatives inhibited inflammatory and microbial activity due to their special structure. These furans can exhibit anti-inflammatory effects through different mechanisms, including suppression of O_2, NO and PGE2 production, regulation of mRNA expression of inflammatory mediators, antioxidant activity through hydroxyl and DPPH-free radicals scavenging activity and reduction of lipid peroxides.[24,44,54] Investigations have shown that the presence of furan and other aromatic rings in the structure of natural furans strongly affects their biological activity.[44,77] Further, enol and phenol moieties together with the hydroxyl group may help to clarify their anti-inflammatory activity.[87,102] The antimicrobial activity of these natural compounds indicated through selective inhibition of microbial growth, suppression of swarming motility and modification of some enzymes. It is evident that different structures of furan derivatives is important for the evaluation of their different biological activities. Hence, it is concluded that anti-inflammatory and antimicrobial effects of furan natural derivatives from different structures warrants further studies to elucidate underlying mechanisms. Further investigations are needed to isolate, detect, and examine the health beneficial effects of different furan derivatives from natural compounds.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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