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Dietary medicine as a gold mine for the discovery of COX-2 inhibitors

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Abstract
Cyclooxygenase-2 (COX-2) inhibitors play key roles in a number of inflammation pathological processes, and cyclooxygenase-2 inhibitors have been developed for anti-inflammatory drugs. In this review paper, the development history of COX-2 inhibitors and the new concepts for the discover of the COX-2 inhibitors from dietary medicine has been summarized. The COX-2 inhibitors from natural sources are including *Sinomenium acutum*, ginger, garlic, tomato, red chill, and tea have been summarized. In addition, the opportunities, challenges and exploring direction of future research on natural COX-2 inhibitors are also discussed.

Keywords: Cyclooxygenase-2 (COX-2), COX-2 inhibitors, natural products, dietary medicine, inflammation

1. Introduction

1.1 Background

Cyclooxygenase (COX), also called prostaglandin H synthase (PGHS), is a bifunctional enzyme. Two main isoforms of COX, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in a variety of cell types and is involved in normal cellular homeostasis. COX-2 is overexpressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck, and esophagus [1].

1.2 Cox-2 related disease and COX-2 inhibitors

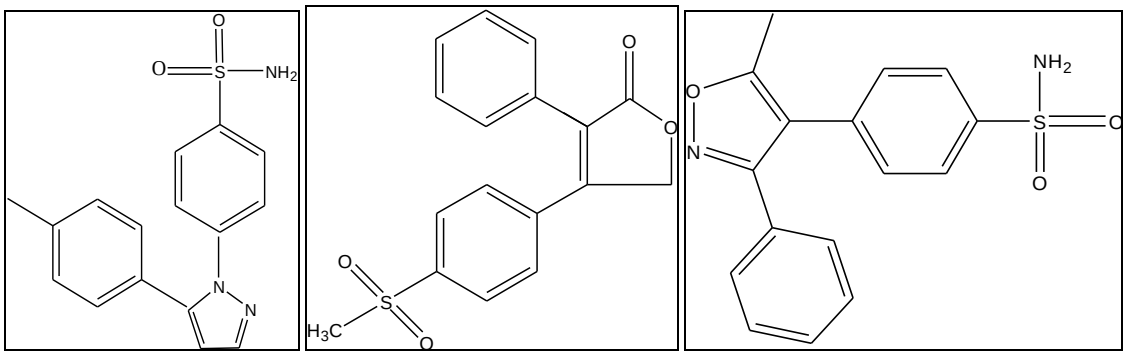
In recent years, overexpression of COX-2 has been reported in various cancer tissues and inflammatory disorders. Therefore, it has been suggested that COX-2 enzyme related to inflammatory and carcinogenesis.

Aspirin, one of non-steroidal anti-inflammatory drugs (NSAIDs), has demonstrated its value as an analgesic, anti-inflammatory, and antithrombotic agent. NSAIDs are of huge therapeutic benefit in the treatment of rheumatoid arthritis and various types of inflammatory conditions. The target for NSAIDs is cyclooxygenase (COX), which is a rate-limiting enzyme involved in the conversion of arachidonic acid into inflammatory prostaglandins. Prostaglandins (PGs) are synthesized by two isoforms of the enzyme PG G/H synthase (cyclooxygenase).Two cyclooxygenase isozymes catalyze conversion of arachidonic acid to prostaglandin H2: constitutive COX-1 and inducible COX-2.Thus, the COX-2 inhibitor plays an important role in the treatment of inflammation.

In about 1990s, a new class of drugs collectively known as selective inhibitors of cyclooxygenase-2 (COX-2) was developed for the treatment of pain and inflammation. Selective COX-2 inhibitors (coxibs) were designed to be at least as efficacious as the common NSAIDs, but were restricted by one of their major side effects, gastrointestinal (GI) bleeding. Since 1998, there are three typical selective COX-2 inhibitors: Celecoxib (Trade name: Celebrex), Rofecoxib (Trade name: Vioxx) and Valdecoxib (Trade name: Bextra) (Fig. 1).

Many researches show that there are several side effects while using COX-2 inhibitor. To start with, the famous drug event of Vioxx, a selected COX-2 inhibitor drug manufactured by Merck. The company withdrew the drug after a study of Vioxx's effect on colon polyps revealed a doubling of heart attacks and strokes from the drug after 18 months of use. Similarity, Bextra, a COX-2 inhibitor made by Pfizer, was also recently shown to cause cardiovascular problems in high-risk patients. Overall, COX-2 inhibitor drugs controversy from its birth, when there has been [2, 3].

Whether we can find some new ingredients, and they have the same functionality with COX-2 inhibitor drugs but can do fix adverse reactions of COX-2 inhibitor drugs. The natural food can be firstly considered to be the target.



(1) Celebrex (2) Vioxx (3) Valdecoxib

Fig 1: Chemical structures of Celecoxib, Rofecoxib and Valdecoxib

2. Dietary medicine

Some dietary components, such as galangin and luteolin, inhibit arachidonic acid peroxidation. All the dietary agents that can suppress these transcription factors have the potential of inhibiting COX-2 expression. Several dietary components including galangin, luteolin, apigenin, 6-hydroxykaempferol, quercetagenin, sasanquol, genistein, wogonin, green tea catechins, curcumin, and resveratrol have been shown to suppress COX-2. Several researchers have reported that many dietary polyphenols inhibit COX activity at the transcriptional level as well as at the enzyme level. While fruits and vegetables are recommended for prevention of many diseases, their active ingredients and their mechanisms of action less well understood [4-6]. The active principle identified in fruit and vegetables and the molecular targets modulated may be the basis for how these dietary agents not only prevent but also treat cancer and other diseases [7].

3. Potential COX-2 inhibitors in dietary medicine

3.1 *Sinomenium acutum*

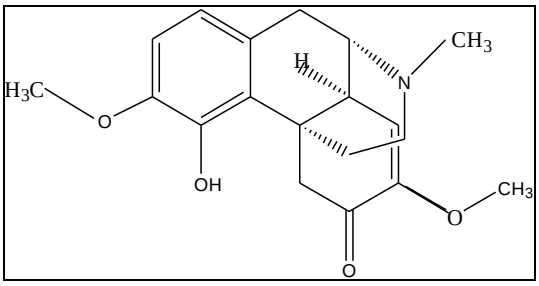


Fig 2: Chemical structure of sinomenine

Sinomenium acutum, an ivy cane of family Menispermaceae, mainly contains alkaloids, such as sinomenine, ethyl sinomenine, sinactine, and others. Sinomenine (SIN) is a type of morphinan alkaloid monomers, also is the main active ingredient in *Sinomenium acutum*, has a variety of pharmacological effects of anti-inflammatory, anti-rheumatic, immunosuppression, analgesia, sedation, etc. The mechanism of the clinical application of SINis related to COX-2.Nuclear factor-kappa B (NF-kB) is an important regulatory molecule in COX-2 gene expression. Many inflammatory cytokines (such as IL-1B, TNFα, etc.) can stimulate tissue cells, NF-kB activity significantly increased, thereby enabling the COX-2 and inducible nitric oxide increases and a large number of synthetic products PGE_2 and NO synthase gene. SIN could significantly inhibit the expression of LPS-induced PG-12 cells of COX-2 and the combine of PGE_2 product, and its mechanism may be realized by SIN inhibiting PC-12 nuclear transcription factor NF-kB activity [8-10].

Sinomenine shows a preferential inhibitory effect on COX-2 over COX-1, These results suggest that Sinomenine is a selective COX-2 inhibitor, which may be directly related to suppressing cyclooxygenase activity [11]. Therefore, sinomenine is a natural cyclooxygenase inhibitor. But the disadvantage of sinomenineinclude side effect, low bioavailability, and short half-life, which is still worthy of future research [12, 13].

3.2Ginger

Curcumin is a natural yellow, orange pigment extracted from turmeric *Curcuma longa* L. Modern science has provided the scientific basis for the use of turmeric against such disorders. Various chemical constituents have been isolated from this spice, including polyphenols, sesquiterpenes, diterpenes, triterpenoids, sterols, and alkaloids. Curcumin, which constitutes 2-5% of turmeric, is perhaps the most-studied component [14]. And the curcumin from ginger can inhibit the rate-limiting enzyme COX-2 in arachidonic acid metabolism pathways [15].

The mechanism is, curcumin was one of the first chemo preventive phytochemicals shown to possess significant COX-2 inhibiting activity through the suppression of NF-kB. Since COX-2-derived prostaglandins stimulate aromatase activity in an organ-specific manner, an independent source of estradiol generation in breast cancer patients undergoing anti-estrogen therapies can be blocked by curcumin and other chemo preventives that have significant COX-2 inhibitory activity. Preclinical studies have shown that curcumin suppresses COX-2 activity through the suppression of NF-kB inducing kinase (NIK) and IkBa kinase (IKK) enzymes [16]. The right amount of food containing ginger which contain curcumin can do effect to the prevention and treatment of inflammation and cancer. It is no doubt that curcumin has gained a spot in the medical world as a potentially effective tool in the fight against inflammation and cancer.

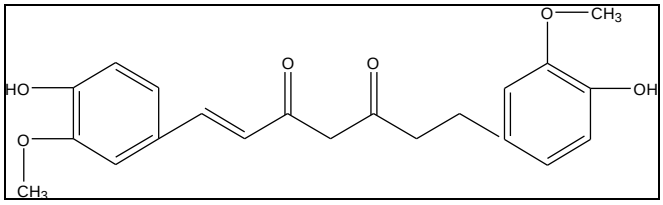


Fig 3: Chemical structures of curcumin

3.3 Garlic

Garlic is a bulbous root of *Allium sativum*, has many pharmacological effects, such as antitumor, antimicrobial and by polipidemic effects [17, 18]. Now that the garlic main

biologically active substances Garlic is a unique organic sulfur-containing compound (OSCs). Garlic derived OSCs are comprised of diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), methyl allyl disulfide (MADS), methyl allyl trisulfide (MATS), 2-vinyl-1-dithiin, and 3-vinyl-1,2-dithiin (Fig. 4). Another research shows a potent platelet aggregation inhibitor, methylallyltrisulfide (MATS), found in the steam-distilled oil components from garlic (*Allium sativum* L.), was showed can affect the COX-2 as the same function of aspirin in inhibiting cyclooxygenase (COX). The arachidonic acid was metabolized at a rate similar to the control. However, a detailed interaction has not yet been demonstrated [19].

COX-2 inhibition by aqueous garlic extract is due to the presence of gamma-glutamylcysteine sulfoxide and other gamma-glutamylcysteines. An interesting alternative explanation has emerged in two recently compounds isolated from raw garlic (both with flavonoid structure): N-feruloyltyramine and thiacremonone that showed a potent inhibitory effect on COX-1 and COX-2. Each garlic preparation has a characteristic chemical composition [20].

Though the comprehensive mechanisms of anti-cancer action of OSCs still remain unclear that needsmore studieson it. Together, these results strongly suggest that the chemo preventive agents present in a garlic-rich diet would have a significant effect on the treatment and prevention of cancer and eat more garlic is good.

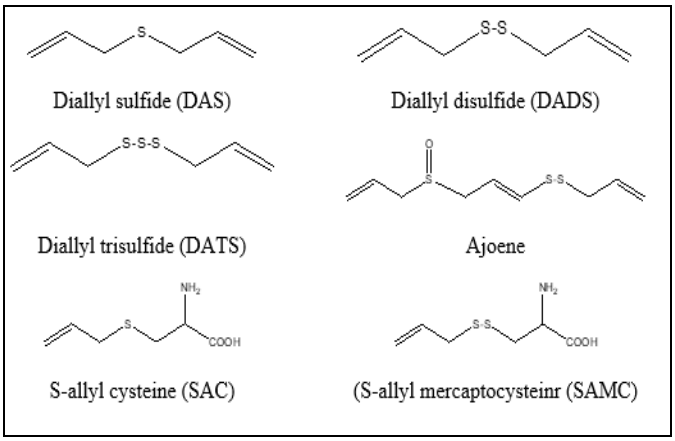


Fig 4: Chemical structures of sulfur-containing compounds in garlic

3.4Red chill

Hot chili pepper is the ripe fruit of Solanaceae and belong to the plant genus *Capsicum* (family Solanaceae) [21].Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) (Fig.6) is a major pungent ingredient of the Capsicum fruits such as hot green and red peppers. Besides its use as a food additive in various spicy cuisines, capsaicin is currently utilized for therapeutic purposes to treat various peripheral painful conditions such as rheumatoid arthritis and diabetic neuropathy [22].

As capsaicin acts on primary sensory neurons, the analgesic effect of capsaicin may be mediated by removing sensitivity of these neurons [23]. For mechanism, there are research show capsaicin in red chill can do effect to COX-2, but the complete mechanism is not clear, and worthy of future research [24, 25].

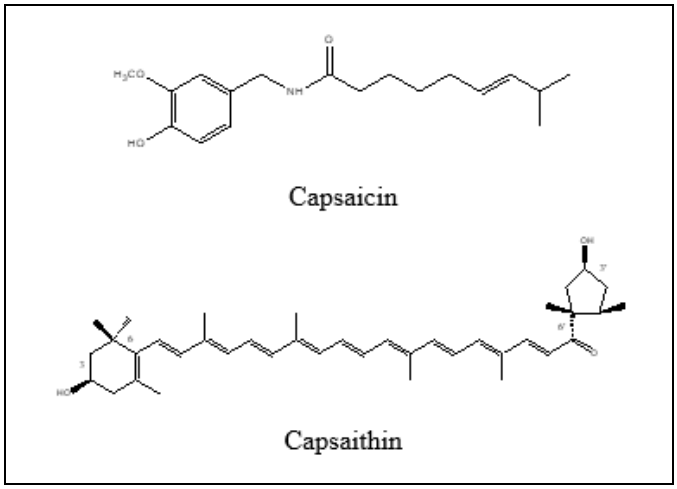
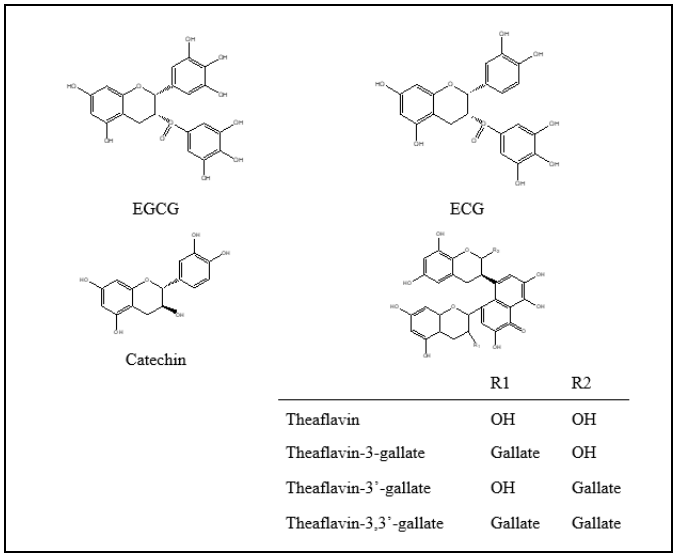


Fig 5: Chemical structures of capsaithin and capsaicin

3.5Tea

Tea has the function of losing weight, and COX-2 protein isthe potential target that tea improves lipid metabolism potential drug [26]. Pretreatment with green tea extract enriched with catechin and EGCG inhibited COX-2 expression induced by TPA in mouse skin. Similarly, EGCG down-regulated COX-2 in TPA-stimulated human mammary cells (MCF-10A) in culture. Both green tea catechin and EGCG displayed COX inhibition in LPS-induced macrophages. Green tea polyphenols EGCG, ECG and theaflavins(Fig. 6) from black tea, also inhibited COX-dependent arachidonic acid metabolism in microsomes from tumors and normal colon mucosa, indicating that tea polyphenols can affect arachidonic acid metabolism in human colon mucosa and colon tumors, perhaps altering the risk for colon cancer in humans.

Tea can modulate TTP mRNA levels in animals and suggest that a post-transcriptional mechanism through TTP could partially account for tea's anti-inflammatory properties. The results also suggest that drinking adequate amounts of green tea may play a role in the prevention of inflammation-related diseases [27]. The EGCG has a similar function with celecoxib, it can do effect to COX-2 which can inhibit inflammation and resistance to the treatment of cancer [28].



	R1	R2
Theaflavin	OH	OH
Theaflavin-3-gallate	Gallate	OH
Theaflavin-3'-gallate	OH	Gallate
Theaflavin-3,3'-gallate	Gallate	Gallate

Fig 6: Chemical structures of catechins in tea

4. Conclusion and prospects

This study reviewed a variety of compounds in fruits and vegetables, which have the similar function to cyclooxygenase inhibitors. Looking cyclooxygenase inhibitors from natural products become the future trend.

In the future, we can provide a natural food supplement made from extracts wherein the food supplement comprises an anti-inflammatory activity that is greater than the anti-inflammatory activity found in the natural fruit or vegetable, as well as we can make an extract that can be presented in a powdered, liquid, or solid form.

The future research about whether fruits and vegetable can replace COX-2 inhibitor must be very meaningful. Because the mostly diseases which need COX-2 inhibitor belong to chronic types. Long-term purpose of selective consumption of fruits and vegetables can be very good in theory, prevent and treat chronic diseases. We eat the food at the same time can prevent disease and improve quality of life, it would be a future of healthy eating best state, it still is a daunting task.

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