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Receptor interactions of constituents of *Zingiber officinalis* and *Solanum lycopersicum* on COX

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Abstract
Cyclooxygenases (COX)-1 and COX-2 are the targets of widely used nonsteroidal anti-inflammatory drugs (NSAIDs) and are essential for such physiological processes as maintenance of the gastrointestinal tract, renal function and fever. COX-1 is expressed constitutively in all tissues, but COX-2 is induced specifically during inflammatory, degenerative, and neoplastic processes. In vitro investigations of ginger (*Zingiber officinalis* Roscoe) preparations and some isolated gingerol-related compounds have shown anti-inflammatory effects of ginger including inhibition of COX. Also, Microglia plays an important role in the immune defense in the central nervous system. Activation of microglia leads to the production of excessive inflammatory molecules and deleterious consequences, including neuronal death. Lycopene, one of the major carotenoids present in tomatoes, has been shown to exert antioxidant properties and to inhibit cancer cell proliferation. It was investigated the signaling pathways involved in lycopene-inhibited expression of cyclooxygenase (COX)-2. Interactions of diclofenac, Gingerol and lycopene were studied on COX-2 receptor by docking them on COX-2 with the help of Molecular Operating Environment software and interactions and receptor binding is reported here.

Keywords: Gingerol, lycopene, cyclooxygenase, receptor binding etc.

Introduction
Inflammation is an vital aspect of host response that leads to infection and injury, and is required to maintain healthy state against bacterial and viral infections. However, extreme or unusual inflammation contributes to several acute and chronic human diseases [1]. However, inflammatory response is characterized by the abundant productions of prostaglandin E2 (PGE2) and thus, these pro-inflammatory mediators are important anti-inflammatory targets [2]. This mechanism is an immunological response following bacterial infection and is primarily mediated by phagocytes macrophages. Prostaglandins are a group of biologically active compounds that play major roles in human physiology in both health and diseases. They function in many different ways and in all major organs. The rate-limiting enzyme in the synthesis of PGE2 is cyclooxygenases (COX). The two most important isoforms of COX have been described: COX-1 and COX-2. COX-1 is expressed constitutively in the majority tissues and is accountable for the homeostatic production of PGE2. In difference, COX-2 is induced by several stimuli, including growth factors, mutagens, pro-inflammatory cytokines and tumor promoters. Its unrestrained activity is thought to play an important role in the pathogenesis of many chronic inflammatory diseases [3]. Besides, subsequent investigations indicated that over expression of COX-2 is often found in many cancers including colon, lung, breast, pancreas and head and neck cancers [4], and is usually associated with poor prognosis and small survival [5]. It is indicated that treatment with selective COX-2 inhibitors may decrease the risk of Alzheimer's [6] and Parkinson's diseases [7] and may also be effectual in the treatment of asthma [8]. Based on these observations, it has been hypothesized that the suppression of PGE2 production in macrophages could serve as the basis for developing potential anti-inflammatory drugs. Meanwhile, from previous studies, non-steroidal antiinflammatory drugs (NSAIDs) that are mainly used in the treatment of pain and inflammation related to a large variety of pathologies have been prepared and marketed[9]. These have been of immense help in the management of various inflammatory conditions like rheumatism, arthritis and breast pain.

Lycopene
Lycopene (from the neo-Latin Lycopersicum, the tomato species) is a red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons, gac, and papayas, but it is not in strawberries or cherries. though lycopene is chemically a carotene, it has no vitamin A activity. Foods which are not red might also contain lycopene, such as asparagus and parsley.

n plants, algae, and other photosynthetic organisms, lycopene is an intermediate in the biosynthesis of many carotenoids, including beta-carotene, which is accountable for yellow, orange, or red pigmentation, photosynthesis, and photoprotection. Like all carotenoids, lycopene is a tetraterpene. It is insoluble in water. Eleven conjugated double bonds give lycopene its deep red color.

Gingerol

Ginger (*Zingiber officinale* Rosc.) belongs to the family Zingiberaceae. It originated in South-East Asia and then used in many countries as a spice and condiment to add flavor to food. Besides this, the rhizome of ginger has also been used in traditional herbal medicine. The health-promoting perspective of ginger is attributed to its rich phytochemistry. Jolad *et al*. grouped fresh ginger into two wide range categories, i.e. volatiles and non-volatiles. Volatiles include sesquiterpene and monoterpenoid hydrocarbons providing the different aroma and taste of ginger. On the differing, non-volatile pungent compounds include gingerols, shogaols, paradols, and zingerone. Ginger has staring potential for treating a number of ailments including degenerative disorders (arthritis and rheumatism), digestive health (indigestion, constipation and ulcer), cardiovascular disorders (atherosclerosis and hypertension), vomiting, diabetes mellitus, and cancer. It also has anti-inflammatory and anti-oxidative properties for controlling the process of aging. Furthermore, it has antimicrobial potential as well which can help in treating infectious diseases. Production of free radicals or reactive oxygen species (ROS) during metabolism beyond the antioxidant capacity of a biological system results in oxidative stress, which plays an important role in heart diseases, neurodegenerative diseases, cancer, and in the aging process. The bioactive molecules of ginger like gingerols have shown antioxidant activity in various modules. Inflammatory disorders such as gastritis, esophagitis, and hepatitis, which are caused not only by infectious agents such as viruses, bacteria, and parasites but also by physical and chemical agents like heat, acid, cigarette smoke, and foreign bodies, are recognized as risk factors for human cancer. Ginger consumption before exercise might reduce naturally occurring quadriceps muscle pain during moderate-intensity cycling exercise. This effect may be due to anti-inflammatory effect of ginger and further investigation need to prove it in human.

Biological activity of Lycopene

Most carotenoids are good antioxidants, quenching singlet oxygen (O2) [10], and trapping peroxyl radicals. O_2 [1] and peroxyl radicals are reactive oxygen species formed endogenously in the process. Both species may react with macromolecules of biological significance, such as DNA, proteins, or lipids, impairing their physiological functions [11] [12]. Such processes are discussed as initial happenings in the pathogenesis of several diseases including cancer, cardiovascular diseases, or age-related macular degeneration. Carotenoids inactivate singlet oxygen through physical or chemical quenching. The efficacy of physical quenching exceeds that of chemical quenching by a large margin (>99.9%) and involves the transfer of excitation energy from 102 to the carotenoid, resulting in ground state oxygen and excited triplet state carotenoid. The energy is distributed between the excited carotenoid and the surrounding solvent to yield a nonreactive ground state carotenoid and thermal energy. In the process of physical quenching the carotenoid remains unaffected, so that it can undergo further cycles of singlet oxygen quenching. The rate constants for the reaction of carotenoids with singlet oxygen are in the range of 10^9 $M^{-1}sec^{-1}$ [13]. The quenching activity of carotenoids closely resembles the number of conjugated double bonds. Lycopene is the most efficient singlet oxygen quencher of the natural caretenoids showing higher quenching rate constants than other C-40 carotenoids [13]. It has been suggested that the increased reactivity is due to the presence of the two additional non-conjugated double bonds. Chemical quenching contributes to less than 0.05% to the overall quenching of [10] O_2 by carotenoids. However, this process, known as photobleaching, is responsible for the final decomposition of carotenoids. Some of the decomposition products formed in the interaction of lycopene with singlet oxygen has recently been identified [14]. Irradiation of Iycopene in the presence of a photosensitizer led to the formation of 2-methyl-2-hepten-6-one and apo-6'-lycopenal as the major reaction products. Methylene blue was used as a sensitizer to study the utilization of carotenoids during photo-oxidation of human plasma and LDL [15]. Lycopene and l3-carotene were more resistant to photooxidation in blood plasma than lutein and zeaxanthin. Upon exposure of blood plasma to a water-soluble [10] O_2 generator, the levels of the lipophilic antioxidants lycopene, β-carotene, and α-tocopherol remained unaffected [16]. The data suggests that carotenoids contribute to the prevention of lipid peroxidation via singlet oxygen quenching. Carotenoids are efficient scavengers of peroxyl radicals, especially at low oxygen tension [17] [18].The interaction of carotenoids with free radicals has been studied using 2,2' -azinobis (3-ethylbenzothiazoline-6-sulfonic acid di ammonium salt (ABTS) as a radical source [19]. Lycopene was the most efficient scavenger of the ABTS-radical followed by cryptoxanthin, lutein, zeaxanthin, and 13- carotene. Astaxanthin and canthaxanthin showed only minor effects. The radical scavenging effect of Iycopene exceeded that of trolox, a water-soluble analog of vitamin E, by a factor of three. Protective effects of lycopene toward oxidative stressmediated damage of the skin were suggested following a study on carotenoid levels in human skin upon irradiation with UV light [20]. When skin was subjected to UV light stress, more skin Iycopene was destroyed than beta-carotene. Because carotenoids are consumed in the process of radical quenching, a preferential protective role of lycopene has been suggested. Tomato leaves methanol extract possesses antiinflammatory activity via inhibition of lipopolysacharide (LPS)-induced prostaglandin (PGE2) [21].

Biological activity of Gingerol

The CO_2 extract from ginger has high polyphenol content. It manifests a very good scavenging of DPPH and reduces its reducing capacity. The extract can be used as an antioxidant at an earlier stage of fat oxidation. The ginger extract shows an antioxidant activity comparable with that of BHT in inhibiting the lipid peroxidation both at 37 C, and at a high temperature of 80 °C. Most inhibited is the stage of formation of secondary products of the auto-oxidation of fats. The ginger extract also shows an inhibiting effect with regard to the hydroxyl radicals, better than that of quercetin. The polyphenols in the ginger extract also demonstrate a higher chelatoforming capacity with regard to Fe^{3+}, leading to the prevention of the initiation of hydroxyl radicals which are known inducers of lipid peroxidation. The properties of the ginger extract under study, compared with the synthetic antioxidant, determine its potential as a natural preservative, applicable in the food and pharmaceutical industries.

Materials and Methods [22, 23]

The computations for docking analysis were carried out on Intel Core-I 3 CPU @ 3.30 GHz workstation, 4 GB memory with windows XP- SP2 operating system and molecular operating environment (MOE 2009.10) as computational software. The co-crystallized protein structure of Cyclooygenase was obtained from protein data bank with PDB code 1PXX MOE identifies favourable poses of flexible ligands in rigid binding sites of macromolecules, typically proteins. MOE offers different routines for conformational sampling, placement and scoring.

The co-crystallized protein structure of Cyclooygenase was obtained from protein data bank with PDB code 1PXX. The crystal structure was then protonated and then the energy was minimised using AMBER99 force filled. The active was generated using atom selector and labelled as 'Binding site'. All the design molecules were built, energy minimised and used as ligands for docking studies using the software. Docking was performed using placements like alpha PMI, alpha triangle and triangle matcher with London dG scoring. Different poses were scrutinised on the basis of suitable interaction and the best molecules were considered for further studies.

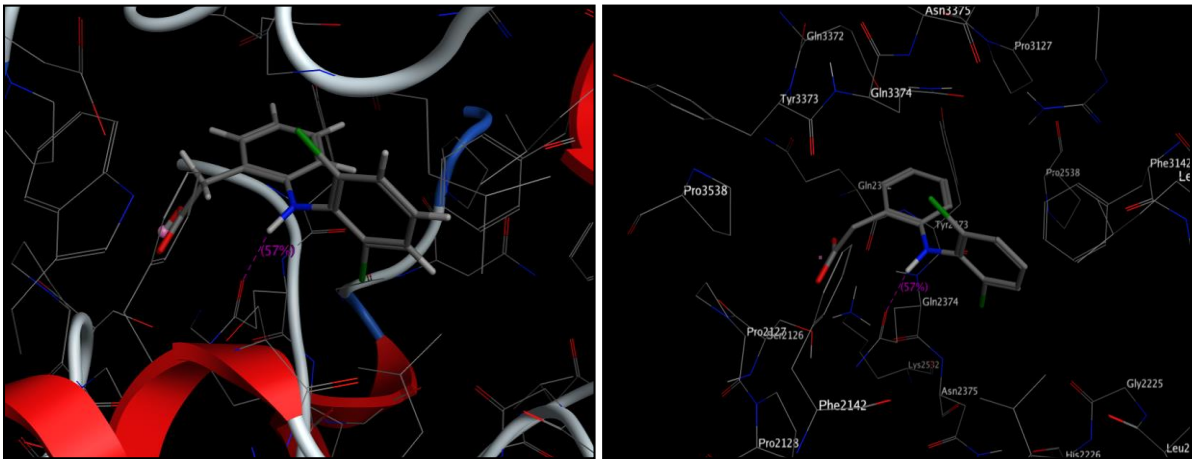
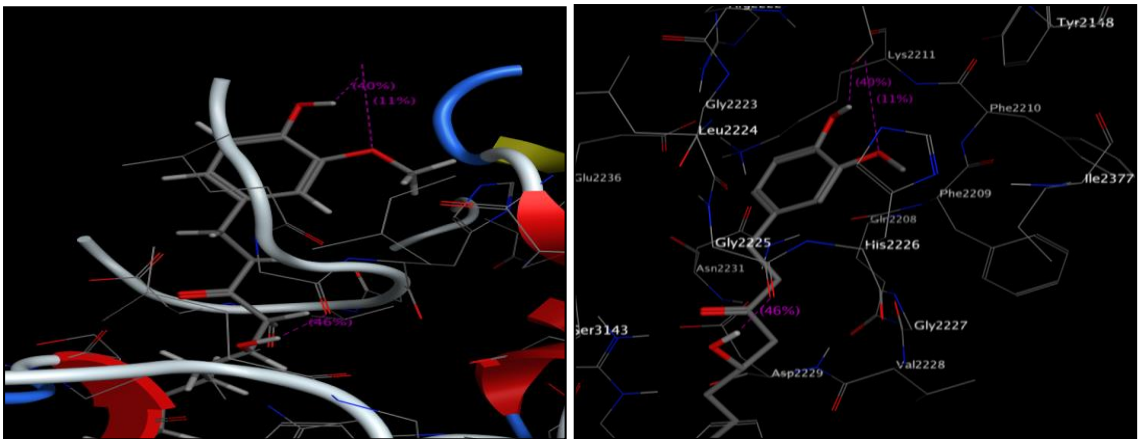
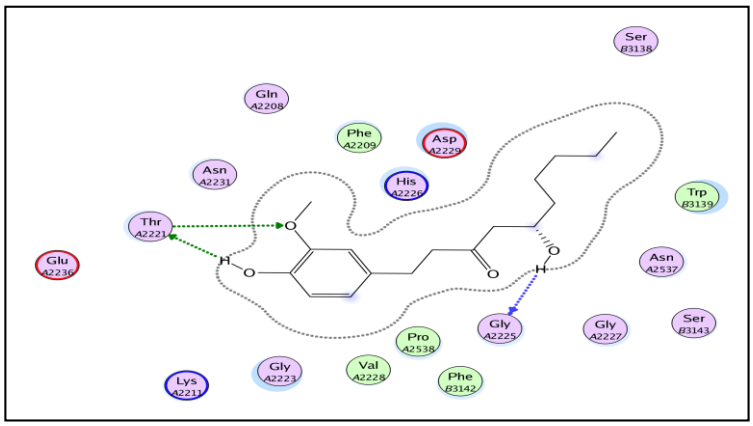


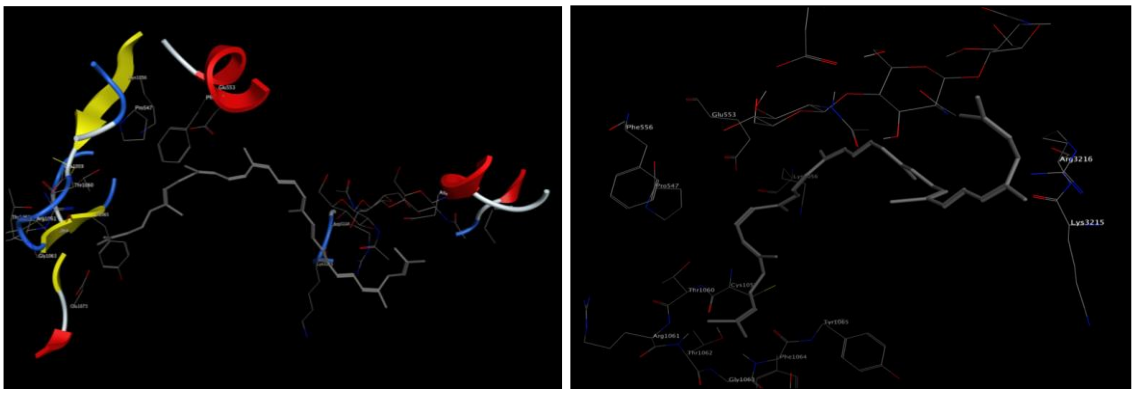
Fig 1: a, b, c indicate interaction of Diclofenac with Cox-2



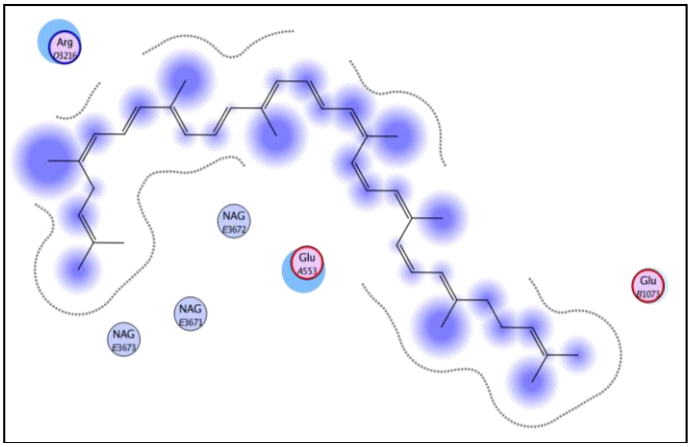


(f)

Fig 2: d, e, f indicate interaction of gingerol with Cox-2



(g) **(h)**



(i)

Fig 3: g, h, i indicate interaction of Lycopene with Cox-2

Result and Discussion

Gingerol and lycopene is well-known for its anti-inflammatory activity. Authors were interested to study interactions of Gingerol and lycopene on COX-2. Interactions diclofenac, Gingerol and lycopene were studied on COX-2 receptor by docking Gingerol and lycopene on COX-2 with the help of Molecular Operating Environment software.

Diclofenac has shown hydrogen bonding polar interaction with Gln A2374 residue of receptor. Also halogen, carbonyl carbon with 57 % receptor binding and few aromatic carbons (highlighted with blue circle) indicates ligand exposure to receptor.

Gingerol has shown hydrogen bonding polar interaction with Thr A2221 residue of receptor with 40 % receptor binding and methoxy group polar interaction with Thr A2221 residue of receptor with 11 % receptor binding. Hydrogen bonding polar interactions observed with Gly A2225 residue of receptor with 46 % receptor binding. Few carbons (highlighted with blue circle) indicate ligand exposure to receptor and acidic and basic interactions.

Lycopene has shown acidic interactions with Glu A553 and Glu B1073 and basic interaction with Arg 03816. Carbons (highlighted with blue circle) indicate ligand exposure to receptor.

Authors would like to conclude here that more receptor binding interactions observed in Gingerol and more ligand exposure is observed in lycopene.

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