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SYNERGISTIC PHARMACOLOGICAL EFFECTS OF PHYTOCHEMICALS DERIVED FROM GINGER, GARLIC AND TULSI

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ABSTRACT: This review article is focused at highlighting the therapeutic values of phytochemicals derived from the natural herbs ginger, garlic and tulsi. It is shown that the phytochemicals derived from these natural herbs work synergistically and exert similar pharmacological profile. The main actions include antioxidant and anti-inflammatory properties. Recommendations are made to follow the antioxidant status at the molecular level. A dietary supplement containing a mixture of 6-gingerol, 6-shogaol, 6-paradol, allicin, ajoene, eugenol and eucalyptol is highly recommended for the ageing patients. There is scope for deriving a common pharmacophore leading to the development of a good anti-inflammatory molecule with reduced side effects which may be beneficial for the elderly with multiple disorders. Information regarding the pharmacological effects and various targets of these phytochemicals has been compiled in the form of tables to provide easy reference for future studies.

INTRODUCTION:

1. Importance of herbal medication:

The commercial drug market is full of a variety of drugs of synthetic and semi-synthetic origin. However, we still look for betterment owing mainly to the side effects. While some side effects are quite harsh, the other may be mild. There have been instances where the side effects have superseded the actual benefits of the drug and could be quite dangerous [1]. There is much less chance of the side effects, if at all, with the herbal medicines. The herbal supplemental medicines work on holistic level, treating the root cause mildly over a long period of time and yielding good results.

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This type of medication is best for people who are allergic to various types of drugs. The natural detoxification process of the body is effectively enhanced by herbal medicines. The slow response of herbal medication appears to be due to the lack of specificity towards the target. Enhancing the specificity aspect of herbal medication without disturbing its pharmacological profile could result in good drugs with fewer side effects. By taking the examples of some natural products popularly used for the cure of common ailments, we will discuss the beneficial effects of ginger, garlic and tulsi and the chemistry and pharmacology responsible for their activities. *Zingiber officinale*, commonly referred as ginger, shows effective hyperglycemic control properties in diabetes mellitus [2]. It is also used to treat a variety of common ailments such as vomiting [3], indigestion [4] and cold-induced symptoms [5]. It is also useful as an anticancer, anti-inflammatory, antioxidant and analgesic agent [6]. Garlic can inhibit and kill bacteria and fungi, lower

the blood pressure, blood cholesterol and blood sugar, prevent blood clotting and exhibit antitumor properties [7]. It can also boost the immune system to fight potential diseases and maintain health [8]. It has the ability to stimulate the lymphatic system which expedites removal of waste products from the body. Its antioxidant character protects cells against free radical damage [9]. It can prevent some forms of cancer, heart diseases, strokes and viral infections [10].

Tulsi, also called holy basil, is a medicinal plant commonly used for cold, influenza, H_1N_1 hepatitis, bronchitis, stress, cancer, headache, heart disease, malaria and digestive disorder [11]. It is a powerful antioxidant, anti-inflammatory agent, immune modulator and repellant for mosquitoes [12]. Use of tulsi increases metabolism and lowers down the stress hormones [13].

It is reflected from the above examples that though these natural herbs possess many medicinal properties they are not specific towards a particular target and, hence, result in low efficacy against each disease. It may be beneficial to construct a common pharmacophore against a few selected targets from these natural compounds and carry it further to derive an appropriate lead compound from a mix of these natural herbs utilizing some semi-synthetic scheme. A good understanding of the bioactive chemical constituents of these herbs and an understanding of their targets at the molecular level is needed. This review article is directed towards such an understanding.

2. Efficiency and utility of multi-target drugs:

Let us first discuss the merits and demerits of multi-target single drugs. The concept of multi-target drug emerged from dealing with debilitating diseases emanating from multiple molecular abnormalities [14-17] where compromise on selectivity was acceptable to attain interference with multiple cellular pathways simultaneously. The charm to proceed in this direction was also backed up by the partial victory against drug resistance problems. In one drug-one target approach, the drug interrupts one particular pathway. It is easy for the body to compensate this by an equivalent pathway which leads to resistance problems. Patients suffering from multiple disorders end up taking a number of medications and have to face the agony of drug-drug interactions. In contrast, multi-target drugs block multiple pathways and, thereby, make it difficult for the resistance to develop by such a mechanism. Multi-target drugs have potential to avoid or reduce side effects arising from the high affinity single therapy [18]. Also, multi-target drugs interact with lower affinity. Thus these drugs do not show unwanted side effects that arise from the high affinity binding of single therapy. These phenomena have been schematically depicted in **Fig. 1**. For example, memantine, an anti-Alzheimer agent, shows that low affinity multi-target drugs might have a lower prevalence and a reduced range of side effects than the high affinity single-target drugs [19-20]. Drugs which bind weakly to several selected targets will achieve a pronounced effect through the synergism of weak interactions. Most multi-target drugs are generally weak binders. Because most of the links in the cellular networks are weak, a low affinity multi-target drug might be sufficient to achieve a significant modulation. This phenomenon is silently depicted by the success stories of the above mentioned herbal drugs during the course of their long term therapies.

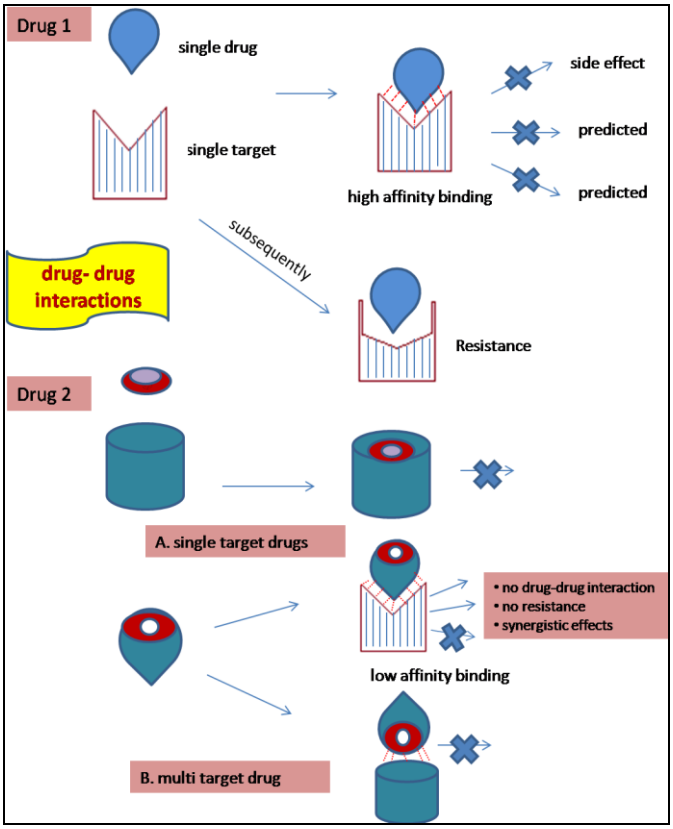

FIG.1: SINGLE TARGET THERAPY VERSUS MULTI TARGET THERAPY

We now discuss the bioactive constituents and pharmacological actions of some common herbs used in our daily diet.

3. Bioactive chemical constituents:

3.1 Bioactive chemical constituents of ginger:

Mojani et al [21] have investigated the bioactive constituents of ginger by using high performance liquid chromatography (HPLC). According to their study, the main bioactive constituents are 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol and 10-shogaol. Bhargava et al [22] have used gas chromatography and mass spectrometry to identify the active constituents of ginger. Their study revealed that ginger has 40 compounds in methanol extract and 32 compounds in ethanol extract. The important constituents out of these are 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, 6-paradol and 8-paradol. Some of the important active constituents are shown in **Fig. 2**.

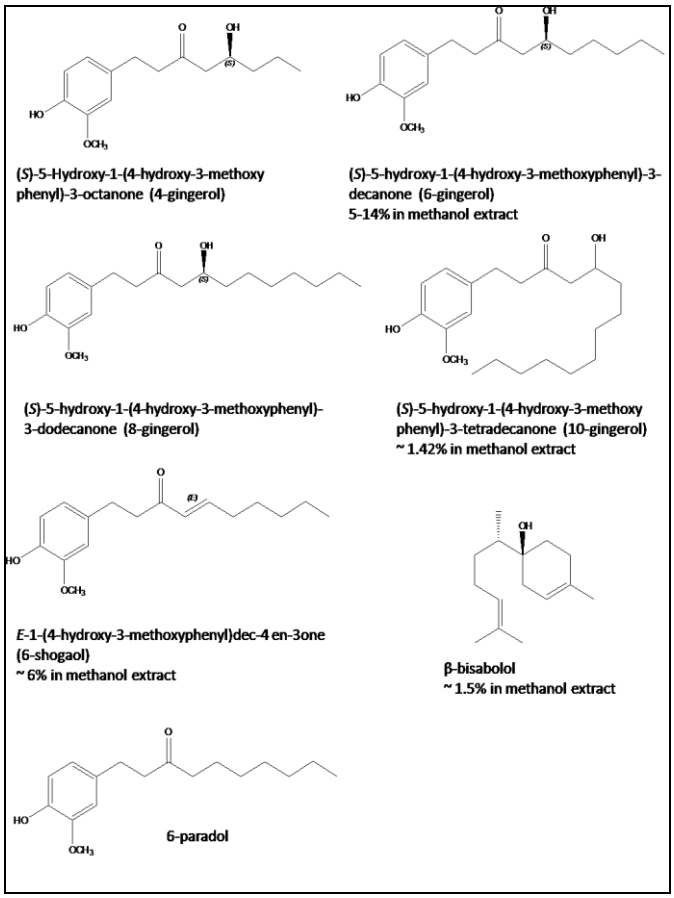

FIG.2: BIOACTIVE CONSTITUENTS OF *ZINGIBER OFFICINALE*

3.2 Bioactive chemical constituents of garlic:

The constituents of garlic vary with the variation in procedure used for the isolation. In most isolation experiments, garlic was found to be enriched in organosulphur compounds. According to Amagase et al [23], garlic has various constituent compounds. Some of these are (*S*)-allylcysteine, alliin, ajoene, alicin, diallyl disulfide, diallyl trisulfide, methylallyl disulfide and vinyldithiins. Some of the important bioactive constituents are shown in **Fig. 3.**

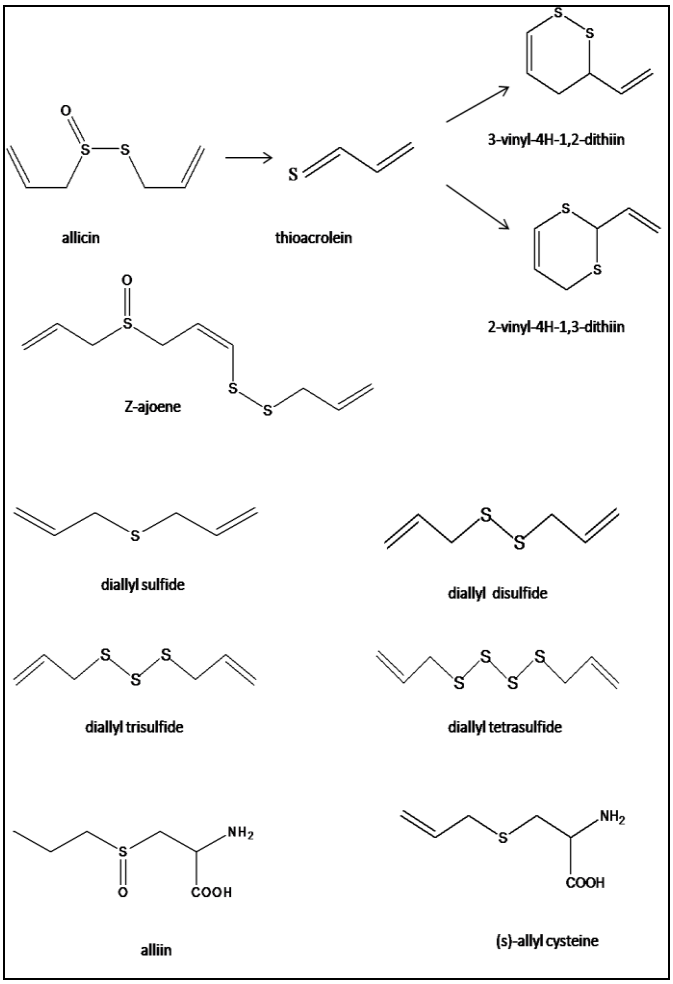

FIG.3: BIOACTIVE CONSTITUENTS OF *GARLIC*

3.3 Bioactive chemical constituents of tulsi:

According to Mondal et al [12], tulsi has a number of constituents. Geraniol, linalool, carvacrol, eugenol, elemol, ursolic acid, rosmarinic acid, vallinin, linaleic acid and linolenic acid are some of the main constituents. Sundaram et al [24] have determined rosmarinic and ursolic acids in the ethanol extract of tulsi leaves by the liquid chromatography-mass spectrometry (LC-MS) method. Garkal et al [25] have extracted eugenol

and analyzed it by gas chromatography. The important constituents of tulsi are shown in **Fig. 4**.

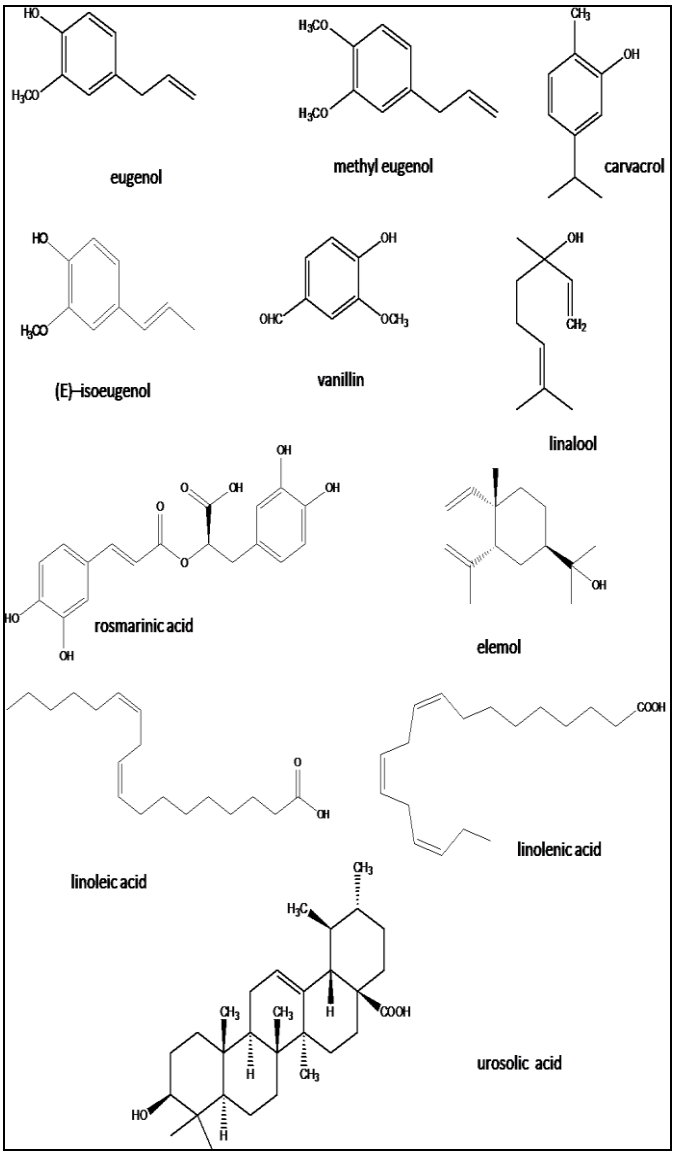

FIG.4: BIOACTIVE CONSTITUENTS OF *HOLY BASIL*

4. Pharmacological actions of ginger:

Several research groups have made efforts to understand the bioactive constituents of ginger and their pharmacological actions. Although ginger extract contains a number of constituents; the gingerol series have been identified as the main active ingredients that contribute to the pungent characteristic smell of ginger extract [26]. In dried ginger powder, shogaol, the dehydrated product of gingerol, is the main pungent constituent. The chemical structures of these components are shown in **Fig. 2** as discussed above. The bioactive constituents of ginger have been shown to have a wide spectrum of pharmacological activities some of which are discussed in following subsections and have been collectively depicted schematically in **Fig. 5**.

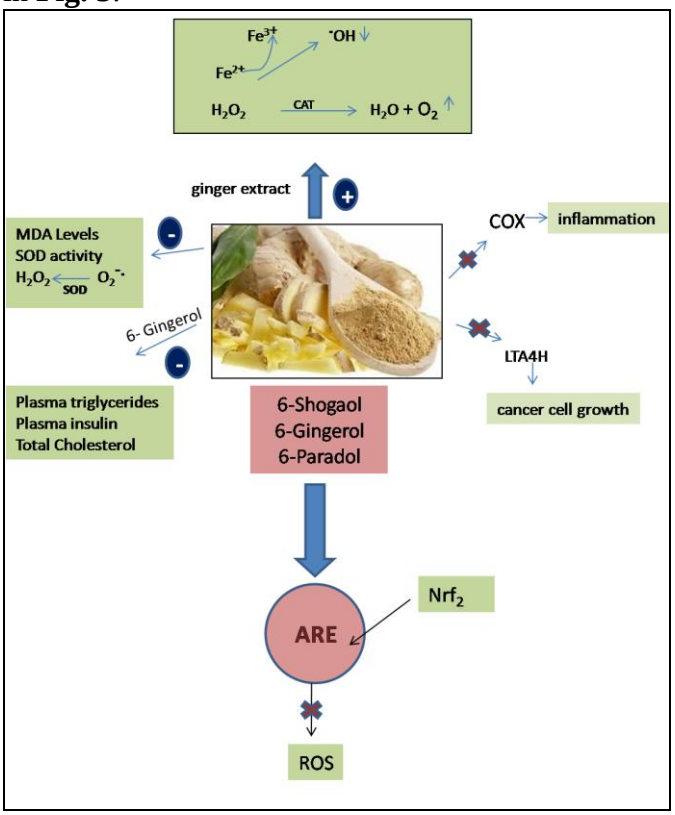

FIG.5: SYNERGISTIC PHARMACOLOGICAL EFFECTS OF GINGER

4.1 Antioxidant activity:

Bak et al [27] have studied the effect of 6-shogaol enriched ginger extract on the antioxidant defense mechanism in mouse models. Their study showed that 6-shogaol rich extract enhanced the antioxidant defense mechanism through induction of the nuclear factor E2-related factor 2 (Nrf2) *in vitro* and *in vivo*. They found that the ginger powder extract with 95% ethanol at 80 °C after drying at 80 °C (GEE8080) displayed much stronger inductions of Antioxidant response element pathway (ARE) reporter gene activity and Nrf2 expression in HepG2 cells than the ginger powder extract with 95% ethanol at room temperature after drying at 80 °C (GEE80RT).

They recommended enhanced usage of ginger along with food in anticipation of free radical production by oxidation of the food stuff. Masuda et al [28] have evaluated the contribution of substituents present on the alkyl chain in gingerols towards the antioxidant activity by the measurement of 1,1-diphenyl-2-picrylhydrazyl

(DPPH) radical scavenging activity, inhibitory effect on oxidation of methyl linoleate under aeration and heating by the Oil Stability Index (OSI) method, and inhibitory effect on the oxidation of liposome induced by 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH). They found that the substituents on the alkyl chain contributed to both the radical scavenging effect and the inhibitory effect of auto oxidation of oils. The inhibitory effect against AAPH-induced peroxidation of liposome was, however, found to be influenced by the alkyl chain length.

Ahmad et al [29] have studied the effect of ginger extract on the oxidant status of rats induced with liver cancer by observing the activity of Superoxide dismutase (SOD), GPx, catalase and the level of malondialdehyde (MDA). Their study showed significant decrease in SOD activity and in the level of MDA while increase was noticed in the catalase activity and no change was observed in GPx. They concluded that the ginger extract increased the antioxidant status in rats as evidenced by the decrease in SOD activity. Shirin et al [30] have compared the antioxidant activity of ginger components (polyphenols, vitamin C, β-carotene, flavonoids and tannins) in different types of solvent extract and water extract by the measurement of DPPH radical scavenging activity, inhibitory effect on oxidation of methyl linoleate under aeration and heating by the OSI method, and inhibitory effect on oxidation of liposome induced by AAPH. The antioxidant activity by these methods was observed to be higher in solvent extracts of ginger than the water extract. Mojani et al [21] have studied the antioxidant activity of ginger by using the DPPH radical scavenging method. They have determined the total flavonoid (TF) and total phenolic contents (TPC) of ginger rhizome by aluminium chloride calorimetric assay and Folin-Ciocalteau reagent. 6-Gingerol was found to be the most abundant component. Methanolic extract of the rhizome of *Zingiber officinale* was used to determine DPPH radical scavenging activity and the result was compared with those of buthylhydroxy toluene (BHT) and α-tocopherol.

4.2 Anti-inflammatory activity:

Saptarini et al [31] have performed in silico docking of 6-gingerol, 6-shogoal and 6-paradol in the binding pockets of COX-1 and COX-2 enzymes. The binding site explored was identical to the binding site for the potent anti-inflammatory drugs flurbiprofen and SC-558. The predicted docking scores, inhibitory constants (K_is) and selectivity index values for the bioactive components of ginger such as 6-gingerol, 6-shogaol and 6-paradol indicated that these molecules are capable of inhibiting the COX-2 enzyme and, thus, they may be classified as anti-inflammatory. Priyarani et al [32] have performed *in vitro* studies for COX inhibitory activities of different solvent extracts of ginger.

They used high performance liquid chromatography to measure the quantity of different constituents. The ethyl acetate extract possessed the highest inhibitory activity. The IC_{50} value for COX inhibition observed in the ethyl acetate extract was 145.04 mg/ml against the standard indomethacin value of 10.2 mg/ml.

Tokuhara et al [33] have used the colorimetric inhibitor screening assay to study the anti-inflammatory activities of 6-shogaol and 6-paradol with reference to indomethacin. Their study concluded that 6-paradol was a better anti-inflammatory agent with IC_{50} value 31.9 mM than 6-shogaol with IC_{50} value 192.7 mM against COX-2.

4.3 Anti-tumor activity:

Jeong et al [34] have used reverse docking in silico approach to reveal that leukotriene A4 hydrolase (LTA4H) protein is a potential target of 6-gingerols. It suppresses anchorage-independent cancer cell growth by inhibiting LTA4H activity in HCT116 colorectal cancer cells. 6- Gingerol effectively prevented tumor growth in vivo in nude mice which was mediated by inhibition of LTA4H activity.

4.4 Anti-depressant activity:

In our body, serotonin receptor subtype 5-HT_{1A} is the main receptor responsible for depression [35]. Ittiyavirah et al [36] have performed in silico studies using Argus lab 4.0.1 software for the docking of gingerol and shogaol to 5-HT_{1A} receptor protein. Gingerol and shogaol interacted with leu 453, phe 454, and tyr 457 residues of the active site. Imipramine was taken as the reference compound

and the docking results were compared against it. The docking scores predicted for shogaol, gingerol and imipramine were -9.03, -8.41 and -8.21 kcal/mol, respectively. They suggested that gingerol and shogaol can act as potent antidepressant compounds.

4.5 Anti-hyperglycemic and lipid lowering effect:

Singh et al [37] have investigated the lipid lowering and blood glucose lowering effect of 6-gingerol in type-2 diabetic db/db mice. They treated db/db mice with 6-gingerol which significantly lowered the blood glucose and improved the glucose tolerance. They found that oral administration of 6-gingerol also significantly decreased the plasma triglycerides, total cholesterol free fatty acid LDL-C and plasma insulin concentration.

5. Pharmacological actions of garlic:

Garlic has also been studied to show a number of pharmacological actions (c.f. **Fig. 6**) similar to ginger as summarized in the following subsections:

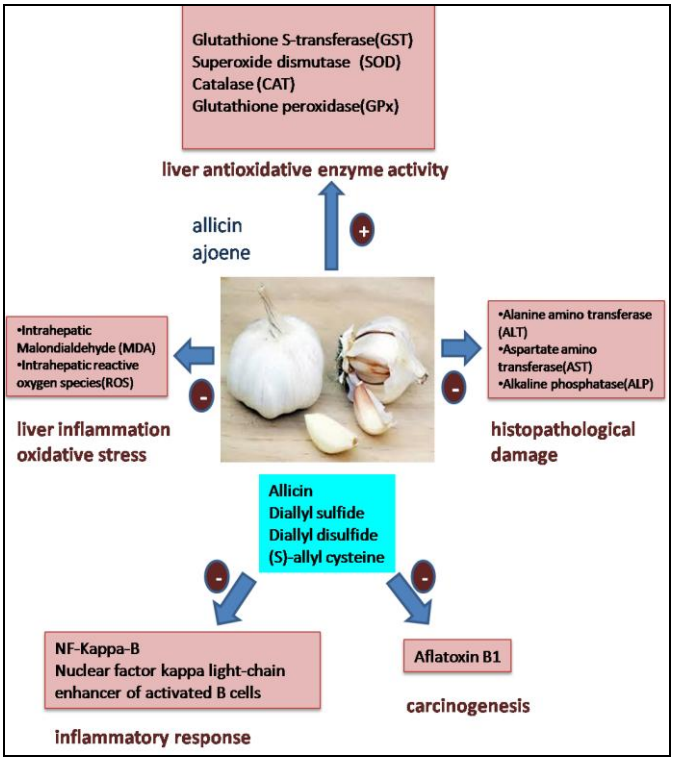

FIG. 6: HEPATO-PROTECTIVE SYNERGISTIC EFFECTS OF GARLIC DERIVED SULFUR CONTAINING PHYTOCHEMICALS

5.1 Anti-oxidant activity:

Prasad et al [38] have studied the ability of allicin content in commercially prepared garlicin to scavenge hydroxyl radical (·OH) using high pressure liquid chromatography (HPLC). The hydroxyl radical was generated by photolysis of H_2O_2 with ultraviolet light and trapped by salicylic acid to produce 2,3- and 2,5-dihydroxybenzoic acids (DHBA). Allicin equivalent in garlicin (1.8, 3.6, 7.2, 14.4, 21.6, 28.8 and 36 micrograms) produced concentration-dependent decrease in the formation of 2,3-DHBA and 2,5-DHBA. The study concluded that the decrease in hydroxyl radical adducts was due to direct scavenging of hydroxyl radical produced from H_2O_2 and not due to scavenging of its adduct products 2,3 and 2,5 DHBA. Allicin prevented lipid peroxidation of liver homogenate in a concentration-dependent manner. These results suggested that the allicin present in garlic scavenges the hydroxyl radical and, thus, garlicin has antioxidant activity [38]. Rahman et al [39] have studied the antioxidant effect of garlic using the DPPH scavenging method. The raw garlic extract showed color change from deep violet to yellow, indicating antioxidant activity against the DPPH radical. On the basis of this study, garlic has been shown to possess antioxidant potential.

Chung et al [40] have studied the antioxidant activity of four main components of garlic, namely alliin, allyl cysteine, allyl disulfide and allicin, prepared by chemical synthesis or purification. Their study showed that the reactivity of these components were not the same for superoxide radical as alliin scavenged superoxide but allyl cysteine and allyl disulfide did not. Allicin suppressed the formation of superoxide by the xanthine/xanthine oxidase system, probably via a thiol exchange mechanism. Further, while alliin, allyl cysteine, and allyl disulfide scavenged the hydroxyl radicals, allicin did not.

Lawrence et al [41] have studied the antioxidant activity of the essential oil isolated from the fresh rhizome of garlic in vitro by DPPH and nitric oxide methods. According to their study, the IC_{50} values for DPPH and nitric oxide scavenging assays were 0.5 mg/ml and 50 µg/ml, respectively. They used BHT and gallic acid as reference. Liu et al [42] have compared the antioxidant activity of garlic aqueous and methanol extracts processed before and after boiling in vitro by ABTS (2, 2'-azino-bis(3-

ethylbenzthiazoline-6-sulfonic acid)) and DPPH (2,2-diphenyl-1-picrylhydrazyl) methods.

5.2 Anti-inflammatory effect:

Keiss et al [43] have shown that garlic powder extract and single garlic metabolites modulate lipopolysachharide (LPS)-induced cytokine level in human blood that leads to an overall inhibtion of NF-kB activity in the surroundings. This contributes to its anti-inflammatory property. Dkhil et al [44] have studied the effects of garlic on coccidiosis caused by Eimeria papillata in male Balb/c mice. This Infection also induced inflammation and injury of the liver which is measured by the decrease in glutathione level and decreased activities of catalase and superoxide dismutase. These infection-induced parameters were significantly less altered during garlic treatment. In particular, garlic counteracted *E. papillata*-induced loss of glutathione and the activities of catalase and superoxide dismutase. It was concluded that garlic treatment significantly attenuated inflammation and injury of the liver induced by *E. papillata* infections.

Ban et al [45] have studied the anti-inflammatory and anti-arthritic properties of thiacremonone, a sulfur compound from garlic, through inhibition of NF-κB because NF-κB is known to be a target of sulfur compounds and also an implicated transcription factor regulating inflammatory response genes. The anti-inflammatory and anti-arthritic effects of thiacremonone were investigated in vivo in 12-O-tetradecanoylphorbol-13-acetate-induced ear edema, carrageenan and mycobacterium butyricum-induced inflammatory and arthritic models. According to their study, thiacremonone suppressed the 12-O-tetradecanoylphorbol-13-acetate-induced ear edema. Thiacremonone was presumed to exert its anti-inflammatory and anti-arthritic properties through the inhibition of NF-κB activation. The sulfhydryl group of thiacremonone was predicted to interact with NF-κB molecules. This property could be exploited for the treatment of inflammatory and arthritic diseases.

Lee et al [46] have studied the anti-inflammatory activity of four garlic constituents, i.e., *Z*- and *E*-ajoene and oxidized sulfonyl derivatives of ajoene. According to their study, the sulfur compounds inhibited the production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) and the expression of the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-1β, and interleukin-6 in LPS-activated macrophages. They analysed, by Western blotting and reverse transcription–polymerase chain reaction, that these sulfur compounds reduced the LPS-induced expression of the inducible NO synthase (iNOS), COX-2 proteins and mRNA. The use of garlic components suppressed the nuclear factor-κB (NF-κB) transcriptional activity and the degradation of inhibitory-κBα in LPS-activated macrophages. The study concluded that *Z*- and *E*-ajoene and their sulfonyl analogs have anti-inflammatory activity.

Bose et al [47] have studied the anti inflammatory activity in carrageenan-induced paw edema in rats. Their study showed that the microwave extracted allicin had the highest potency against carrageenan-induced inflammation in rat paw. They also revealed that both the bath and probe sonication extracted allicin had anti-inflammatory properties. However, while the bath sonication extracted allicin had linear potency like simple maceration extracted allicin, the probe sonication extracted allicin had decreasing order of percentage inhibition of the carrageenan-induced inflammation in rat paw.

5.3 Anti-tumor activity:

A glycoprotein of about 14kDa molecular weight was isolated from the garlic extract and its antitumor activity was assessed. It induced natural killer augmentation against K562 tumor cell line. In vivo studies confirmed that the garlic extract, partially purified by ultra filtration and further purified by chromatography, could indeed induce resistance to the growth of spontaneous mammary carcinoma in balb/c mice [48].

5.4 Anti-hepatotoxicity activity:

It is a potent drug for the treatment of alcoholic liver disorders and also in hepatotoxicity caused by CCl_4. Abd et al [49] have explained the effect of garlic oil on hepatotoxicity induced by the intubation of CCl_4 in both sex rabbits. Their study showed that the use of garlic oil produced significant reduction in the levels of alanine aminotransferase (ALT), aspartate

aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin. The use of garlic oil was found to revert the liver tissue to the normal state. According to Mirunalini et al [50], oral supplementation of two small size raw garlic cloves to alcoholic patients for 45 days had significantly decreased the activity of liver marker enzymes ALT, AST and ALP, and also decreased the level of lipid peroxidation and enhanced the antioxidant status near to normal.

5.5 Immuno-modulator effect:

Kyo et al [51] have studied the effect of aged garlic extract (AGE) on the immune function. They showed that AGE reduced the antigen-specific ear swelling caused by picryl chloride ointment and intravenous administration of anti-trinitrophenyl antibody in the immunoglobulin (Ig) E-mediated allergic mouse model.

As discussed above phytochemicals present in garlic exert a number of pharmacological effects. However, these effects are highly hepato-protective and work synergistically to protect from liver damage as depicted in **Fig. 6**.

6. Pharmacological actions of tulsi:

Similar to ginger and garlic, tulsi (holy basil, *Ocimum sanctum, Ocimum tenuiflorum*) is an important medicinal herb and shows a number of pharmacological effects as described in sections below.

6.1 Anti-oxidant activity:

Sethi et al [52] have explored the antioxidant action of tulsi by monitoring the levels of superoxide dimutase, gluthiones and thiols. Significant reduction in peroxidised lipid level was observed. Deo et al [53] have studied the antioxidant activity of methanolic and ethanolic leaf extracts of Krishna Tulsi (*Ocimum tenuiflorum*) using DPPH-induced radical scavenging method and Ferric reducing antioxidant power (FRAP) method and compared the results with the standard antioxidant ascorbic acid. The study showed that the extract of *Ocimum tenuiflorum* has the highest antioxidant activity. Balaji et al [54] have studied the antioxidant activities and total phenolic assay of *Ocimum tenuiflorum* using butylated hydroxyl toluene (BHT) radical scavenging activity method and DPPH-induced radical scavenging method with ascorbic acid as a standard antioxidant. Their study showed that the leaf extract has more antioxidant activity than the stem extract towards superoxide anion radical. The leaf extract was found to contain higher quantities of carotenoids and ascorbic acid than the stem extract.

Kath et al [55] have studied the antioxidant activity of hydroalcoholic extract of *Ocimum sanctum* leaves in animal models of peptic ulcer by estimating plasma MDA levels. The animal models used were ethanol-treated rats and histamine-treated guinea pigs. The study showed that the tulsi leaf extract significantly decreased the MDA level in both the animal groups. The extract also increased the SOD levels in pyloric ligated rats and histamine-treated guinea pigs. Ramesh et al [56] have studied the antioxidant activity of hydroalcoholic extract of tulsi leaves against cadmium-induced damage in albino rats. Their study showed that intake of tulsi leaf extract significantly decreased the lipid peroxidation (LPO) level and increased SOD, CAT, GPx, Reduced Glutathione (GSH) and Vitamin C (Ascorbate) levels. The study also revealed that tulsi leaves possess antioxidant activity.

6.2 Anti-inflammatory activity:

Kalabharathi et al [57] have studied the anti-inflammatory activity in fresh tulsi leaf paste. In vivo anti-inflammatory activity was studied in animal models using carrageenan-induced paw edema. Tulsi paste was fed to the animal model one hour before administration of the phlogistic agent. Significant anti-inflammatory property was observed. Thakur et al [58] have studied anti-inflammatory activity of the essential oil extract of tulsi leaf (Eugenol) in wistar rats by using carrageenan-induced Hind paw edema method. They also compared it with the anti-inflammatory activity of the standard paracetamol. Their study showed that the extracted eugenol and paracetamol exhibited significant activity when compared with carrageenan control.

Manaharan et al [59] have reported anti-inflammatory activity in *Ocimum sanctum* essential oil. Mirje et al [60] have studied anti-inflammatory activity of tulsi alone and in combination with indomethacin using Carrageenan-induced rat paw edema. The study

showed that the aqueous extract of tulsi had significant anti-inflammatory effect. Also, the reduction of edema by tulsi was found to be better than that of the standard anti-inflammatory drug, indomethacin. The authors predicted that the anti-inflammatory activity of tulsi was due to inhibition of both cyclooxygenase and lipooxygenase pathways of arachidonic acid metabolism. Based on the study of anti-inflammatory activity of *Ocimum sanctum*, Singh et al [61] have concluded that linolenic acid present in it inhibited both the cyclooxygenase and lipooxygenase pathways of arachidonic acid metabolism which resulted in the anti-inflammatory activity.

6.3 Anti-tumor activity:

Karthikeyan et al [62] have investigated the medicinal effect of tulsi on human fibrosarcoma cells (HFS) in culture. They found that the intake of aqueous and ethanolic extracts of tulsi by mice bearing the sarcoma-180 solid tumors mediated significant reduction in tumor volume.

6.4 Anti-stress activity:

Anju [63] has performed *in vivo* studies on male swiss albino mice. Mice that were fed with the ethanolic extract of tulsi leaves exhibited significant anti-stress and adaptogenic activity. The pharmacological and pathological effects observed on administration of tulsi leaf extract are depicted in **Fig. 7**. Tulsi leaf extract shows profound antioxidant effect.

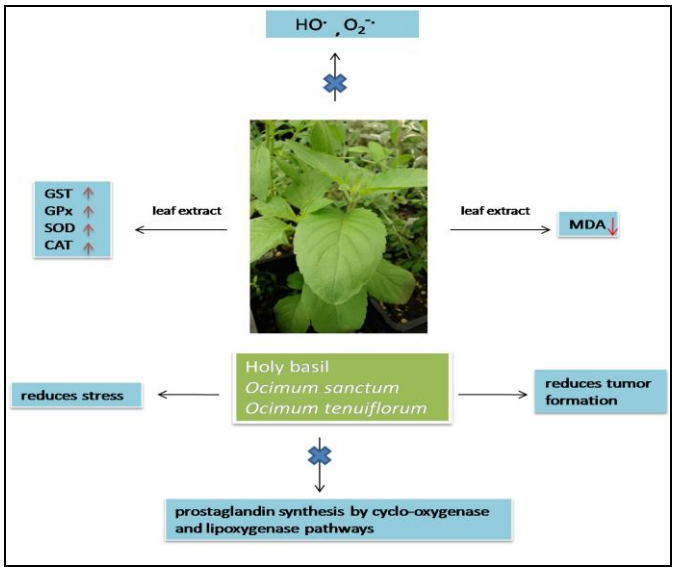

FIG.7: SYNERGISTIC PHARMACOLOGICAL AND PATHOLOGICAL EFFECTS OBSERVED BY THE ADMISTRATION OF TULSI LEAF EXTRACT

7. Molecular modeling and docking studies:

This section is specifically focused at the past in silico attempts at understanding the mode of action, at the molecular level, of phytochemicals derived from ginger, garlic and tulsi. Since these phytochemicals are multi-target entities, it is important to understand which targets have been probed so that the future in silico work may follow fruitful directions.

7.1 Molecular modeling and docking studies with ginger components:

Some molecular modeling and docking studies with ginger components have already been mentioned in sections 3.2 to 3.4 [31, 34, 36]. These studies have demonstrated that the ginger component 6-gingerol can inhibit COX-2, leukotriene A4 hydrolase protein and serotonin receptor subtype 5-HT_{1A}. 6-Gingerol thus appears to be the main bioactive constituent responsible for many therapeutic benefits of ginger. Lee et al [64] have shown the anti-inflammatory properties of 1-dehydro-[10]-gingerdione by inhibiting 1KKβ activity. Compound-1KKβcomplex was studied in silico combined with in vitro studies. Le [65] has studied the binding of six main constituents of ginger with the proteins associated with glucose metabolism such as Glutamine fructose-6-phosphate aminotransferase (GFAT), 11-β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), Mono ADP-ribosyltransferase sirtuin-6 (SIRT6), Glucose transporter type 4 (GLUT4) and Glycogen phosphorylase. He has concluded that the components β-bisabolol and 10-gingerol had low activity. He has emphasized that a mixture of all components be used for drug development.

Liu et al [66] have studied the apoptotic effects of 6-shogaol in silico by docking it in elF2β. Their study has indicated interaction of 6-shogaol with ser 51 at the N-terminal domain. These results were validated by immunoblotting assay studies. Mishra [67] has performed docking of virtually screened geraniol derivatives into tyrosine kinase receptor for the anticancer activity and concluded that the geraniol derivatives had better druggability. Azam et al [68] have performed in silico docking studies of ginger components at acetylcholinesterase enzyme. Docking studies performed using Auto dock 4.2

software has highlighted the features required for inhibiting acetylcholinesterase enzyme.

7.2 Anti-carcinogenic activity of garlic constituents:

Prabahar et al [69] have performed in silico studies on allicin and ajoene constituents of garlic for their inhibitory effects on aflatoxin biosynthesis. Models for fifteen enzymes involved in aflatoxin biosynthesis were generated, assessed and validated. Docking of allicin, ajoene and a small molecule inhibitor designed from these two, namely ajocin was performed at fifteen enzymes after identifying binding sites with the help of Q Site finder. The key role in toxin synthesis is played by Versicolorin B synthase. The components of garlic were found to significantly inhibit carcinogen synthesis.

7.3 Identification of ajoene targets:

Deshmukh et al [70] have used in silico reverse screening approach to identify molecular targets for ajoene and subsequently performed docking studies for validation. Ajoene was predicted to perform comparable to the native ligand at 59 therapeutically interesting targets, including the anti-inflammatory and anti-hypertensive targets. It was thus anticipated that garlic may be used as a nutraceutical in many diseases.

7.4 Molecular modeling and docking studies with tulsi components:

The bioactive components of tulsi such as linalool, eugenol and eucalyptol are largely hydrophobic compounds. Lawtrakul et al [71] have performed DFT B3LYP/6-31G(d) calculations to study encapsulation of the bioactive components of tulsi by β-cyclodextrin in the gas phase and also in the aqueous phase to enhance their solubility while retaining the pharmaceutical values.

The study concluded that β-cyclodextrin forms 1:1 complexes with the bioactive components (linalool, eugenol, methyl eugenol, estragole, eucalyptol) present in essential oils from tulsi by utilizing electrostatic dipole-dipole, van der Waals and hydrophobic interactions. They also concluded that the differences in the binding affinities and the conditions for binding could be utilized to design an appropriate separation technique for the bioactive constituents of tulsi. Azeez et al [72] have docked various phytochemicals at glutathione-S-transferase (GST) of filarial nematodes. Alongwith other phytochemicals, various constituents of tulsi such as eugenol, methyl eugenol, methyl-isoeugenol, isoeugenol and linalool were shown to inhibit GST and, thus, act as leads for development of drugs for lymphatic filariasis. Dhivya and Manimegalai [73] have also suggested the use of linalool as a mosquito control agent as it can bind with the odorant binding protein 2 L2C of *Culex quinquefasciatus* species. Sadeghian et al [74] have docked eugenol esters at 15-lipoxygenase enzyme and suggested that they could be used to derive drugs for pulmonary diseases and anti-inflammatory drugs.

8. Critical evaluation of pharmacological profile of phytochemicals under study:

It is clear from the above discussions that the phytochemicals derived from ginger, garlic and tulsi possess antioxidant activity. The main among these phytochemicals are 6-gingerol, 6-shogaol, 6-paradol, allicin, ajoene, eugenol and eucalyptol. These chemicals up-regulate the activities of Catalase, Superoxide dismutase, Glutatione peroxidase and Glutathione-S-transferase. However, the details of this up-regulation at the molecular level are not clear. Questions arise as to whether these chemicals are agonistic and work analogous to the natural substrate or they up-regulate the activity in an indirect fashion. The reduction in stress, hypertension and risk of cardiovascular related diseases follows naturally.

The other most significant pharmacological effect of the phytochemicals from the three herbs is the anti-inflammatory effect. These phytochemicals reduce inflammation induced by many disorders and, of course, induced directly due to injury, trauma, etc. The anti-inflammatory effect is due to inhibition of prostaglandin synthesis or down-regulation of the gene responsible for the inflammatory response. These are overall multi-targeted phytochemicals. Their agonistic or antagonistic activities and their interactions with different receptors at the molecular level are still poorly understood. We have summarized the pharmacological actions of these specific phytochemicals or the whole herbal extracts in

Table 1 as reported by various researchers in the field. To assist in silico research on these phytochemicals, we have collected relevant RCSB protein databank entries in **Table 2** for quick reference. We hope that these two tables will provide an overview of the experimental and in silico work done on these important herbal medications and, at the same time, also provide impetus for research in this area with a quick start.

TABLE 1: PHYTOCHEMICALS AND THEIR OBSERVED PHARMACOLOGICAL ACTIONS

Natural herb / Phytochemical	Pharmacological action	Reference
Phytochemicals from ginger		
Ginger extract	Induction of Nrf2 and ARE gene activity	27
Ginger extract	Decrease in MDA level Increase in CAT activity	29
Ginger extract	Radical scavenging activity	30,21
Components of ginger (6-gingerol, 6-shogaol 6- paradol)	COX inhibitory activity	31,32,33
6- gingerol	Inhibition of LTA4H activity	34 (CADD)
Gingerol, shogaol	Inhibition of 5-HT_{1A}	36(CADD)
6- gingerol	Decrease in plasma triglycerides, total cholesterol, Plasma insulin	37
10- gingerdione	Inhibition of 1KKβ activity	64(CADD)
Ginger extract	Inhibition of GFAT 1/β – HSD1,S1RT6,GLUT4	65(CADD)
6- shogaol	Inhibition of elF2α	66
Geraniol derivative	Inhibition of Tyrosine kinase receptor	67(CADD)
Ginger components	Inhibition of AChE	68 (CADD)
Phytochemicals from garlic		
Garlic extract (Allicin)	Radical scavenging activity	38,39
Alliin	Superoxide scavenging	40
Allicin	Superoxide scavanging	40
Allyl disulfide, allyl cysteine , alliin	·OH radical scavenging	40
Garlic extract (aqueous, methanolic)	Antioxidant activity	41,42
Garlic powder	Inhibition of NF-βB activity	43
Garlic extract	Hepato- protective activity	44
Thiacremonone from garlic	Inhibition of NF-βB activity (anti-inflammatory, anti-arthritic)	45
Ajoene (Z,E and oxidized sulfonyl derivatives)	Inhibition of NF-βB activity	46
Microwave extracted allicin	Anti-inflammatory	47
Glycoprotein from garlic extract	Anti tumor activity	48
Garlic oil and garlic cloves	Reduced levels of ALT, AST, ALP (Hepato- protective effect)	49,50
Aged garlic extract	Immune modulator effect	51
Allicin, ajoene	Inhibition of versicolorin B synthase involved in aflatoxin biosynthesis	69 (CADD)
Ajoene	Identification of targets (Reverse docking)	70
Phytochemicals from tulsi		
Tulsi extract	Reduced peroxidised lipid levels	52
Methanolic /Ethanolic leaf extract	Antioxidant activity	53,54
Hydroalcoholic extract of tulsi leaves	Decreased MDA levels	55
Hydroalcoholic extract of tulsi leaves	Decreased lipid peroxidation, increased SOD, CAT, GPx activity	56
Tulsi leaf paste	Anti-inflammatory activity	57
Eugenol	Anti-inflammatory activity	58,59
Aqueous extract of tulsi	Anti-inflammatory activity	60
Ocimum sanctum fix oil	Inhibition of COX and lipoxygenase pathways	61
Aqueous and ethanolic extract of tulsi	Reduction in solid tumors	62
Ethanolic extract of tulsi	Anti stress activity	63
Bioactive components of tulsi	Encapsulation of bioactive component by β-cyclodextrin	71(CADD)
Various phytochemicals from tulsi	Inhibition of GST	72(CADD)
Linalool	Binding with odorant binding protein of C. quinquefasciatus	73(CADD)
Eugenol esters	Inhibition of 15-lipoxygenase enzyme	74(CADD)

TABLE 2: SUMMARY OF AVAILABLE TARGET STRUCTURES OF STUDIED PHYTOCHEMICALS FOR FURTHER COMPUTER AIDED DESIGNING STUDIES

Year of pdb release	RCSB protein data bank entry ID	Content
Targets involved in hepatotoxicity		
Alkaline phosphate (ALP)		
1999	1B8J	Alkaline phosphatase complexed with vanadate
1996	1ANJ	Alkaline phosphatase (K328H)
1996	2ANH	Alkaline phosphatase (D153H)
Aspartate aminotransferase (AST)		
1997	1IVR	Structure of aspartate amino transferase

1994	1MAP	Crystal structure of true enzymatic reaction intermediate: Aspartate and glutamate ketimines in aspartate amino transferase
1994	1MAQ	Crystal structure of true enzymatic reaction intermediate: Aspartate and glutamate ketimines in aspartate amino transferase
		Alanine aminotransferase (ALT)
2010	3LQS	Complexe structure of D- amino acid aminotransferase and 4-amino-4,5-dihydro thiophene carboxylic acid(ADTA)
2009	3A8U	Crystal structure of omega- amino acid : pyruvate amino transferase
2000	1G2W	E1775 mutant of pyridoxel-5'-phosphate enzyme D- amino acid amino transferase
		Sirtuin - 6
2011	3PKJ	Human SIRT 6 crystal structure in complex with 2'-N-Acetyl ADP ribose
2011	3PKI	Human SIRT 6 crystal structure in complex with ADP ribose
2009	3K35	Crystal structure of human SIRT-6
		Glutamine-fructose-6-phosphate aminotransferase (GFAT)
2015	4S1W	Structure of a putative glutamine-fructose-6 phosphate amino transferase from staphylococcus aureus subsp. Aureus Mu50.
2013	4AMV	E. coli glucosamine-6p synthase in complex with fructose-6R
2011	3TBF	C- terminal domain of glucosamine-fructose-6-phosphate amino transferase from francisella-tularensis.yg ll
		Targets involved in antioxidant activity
		Nuclear factor E2-related factor 2
2013	3WN7	Crystal structure of the Keap 1 protein in complex with the n-terminal region of the Nrf2 transcription factor
2012	2LZ1	Solution NMR structure of DNA- binding domain of human NF-E2-related factor 2 , north east structural genomics consortium target HR3520O
2007	2DYH	Crystal structure of the Keap 1 protein in complex with the n-terminal region of the Nrf2 transcription factor
		Superoxide dismutase (SOD)
2002	1GV3	The 2.0 Å resolution structure of the catalytic portion of a cyanobacterial membrane bound maganese superoxide di mutase
1999	2APS	Cu/Zn super oxide di mutase from aceteno bacillus pleuropneumoniae
1994	1IDS	X- ray structutre analysis of iron dependent superoxide dismutase from mycobacterium tuberculosis at 2.0 Å resolutions reveals novel dimer interactions
		Catalase (CAT)
2013	4B7G	Structure of a bacterial catalase
2013	4B7F	Structure of a liganded catalase
2013	4B7H	Structure of a high dose liganded bacterial catalase
		Glutathione peroxidase (GPx)
2009	2WGR	The case of Schistoma mansoni phospholipid glutathione peroxidase.
2007	2R37	Crystal structure of human glutathione Peroxidase 3
2007	2OBI	Crystal structure of the selenocysteine to cysteine mutant of human phospholipid hydroperoxide glutathione peroxidase(GPx4)
		Targets involved in tumor activity
		Leukotriene A_4 hydrolase (LTA_4H)
2015	5AEN	LTA_4H complexed with inhibitor dimethyl 1 (2-(4- phenoxy phenoxy)ethyl) amine
2014	4MS6	LTA_4H complex with pro-gly-pro analogue
2013	4DPR	Structure of LTA_4H in complex with inhibitor captopril
		Targets involved in inflammation
		Cyclo-oxygenase (COX)
2012	3KRK	Structure of archidonic acid bound in the cyclo-oxygenase channel of L531F murine COX-2
2012	4FM5	Structure of des- methyl fluribiprofen bound to murine COX-2
2010	3RR3	Structure of (R)- fluribiprofen bound to murine COX-2
		Targets involved in depression
		5-hydroxytryptamine (serotonin) receptor 1A ($5HT_1A$)
2014	4OAJ	Crystal structure of complexed between SAP97, PDZ2 and 5HT2A receptor peptide.
2014	4PIR	X- ray structure of mouse serotonin 5-HT3 receptor
2013	4IAR	Crystal structure of the chimeric protein 5-HT1B-BRIL in complex

		with ergotamine (PSI community target)
		Enzymes involved in acetylcholine breakdown
		Acetylcholine esterase (AChE)
2015	4PQE	Crystal structure of human acetylcholine esterase
2014	4QWW	Crystal structure of Fab410-BFAChE complex
2014	4TVK	Torpedo California acetylcholine esterase in complex with a chlorotacrine – juglone hybrid inhibitor.

In light of the pharmacological actions summarized in **Table 1**, it is recommended that a synthetic dietary supplement be designed combining 6-gingerol, allicin and eugenol for ageing patients to reduce oxidative stress, radical overload and CNS-related diseases pertaining to the old age. A common pharmacophore from the bioactive constituents of the three herbs may also be derived as a prospective lead compound for the development of a good anti-inflammatory compound without side effects. Inflammation accompanies many disorders and retaining the multi-targeted nature of these phytochemicals may prove to be of significant value.

CONCLUSION: To summarize, this review article has highlighted the therapeutic value of phytochemicals derived from ginger, garlic and tulsi. These phytochemicals are multi-targeted but exert synergistic effects that may be utilized in several disorders. Combining these phytochemicals to derive a dietary supplement would be of great value to ageing patients. In addition, a common pharmacophore derivation may help derive a lead compound for good anti-inflammatory drug required in several disorders. The review article presents a comprehensive view of the past experimental and in silico research on the topic. This will aid in better utilization of multi-targeted nature of these phytochemicals and will help researchers focus on targets of interest.

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