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Review

Biomedical Effects of Popular Phytonutrients and Their Phytochemicals: A Comprehensive Review

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Featured Application: This review is significant to the researchers using plant-derived products as therapeutics. It evaluates and summarizes the most recent studies published in the last 20 years and combines the latest botanical description, pharmacological, and biomedical effects of the most popular phytonutrients and their active phytochemicals. Furthermore, this review provides the reading audience fast, summarized information of >250 scientific articles on the most utilized phytonutrients worldwide, of which much tertiary literature is found without the support of robust, reproducible scientific data.

Abstract: Phytonutrients are plant foods that contain many natural bioactive compounds, called phytochemicals, which expose specific biological activities. These phytonutrients and their phytochemicals may play an important role in health care maintaining normal organism functions (as preventives) and fighting against diseases (as therapeutics). Phytonutrient's components are the primary metabolites (i.e., proteins, carbohydrates, and lipids) and phytochemicals or secondary metabolites (i.e., phenolics, alkaloids, organosulfides, and terpenes). For years, several phytonutrients and their phytochemicals have demonstrated specific pharmacological and therapeutic effects in human health such as anticancer, antioxidant, antiviral, anti-inflammatory, antibacterial, antifungal, and immune response. This review summarizes the effects of the most studied or the most popular phytonutrients (i.e., turmeric, garlic, cinnamon, graviola, and oregano), and any contraindication found. This article also calculated the physicochemical properties of the main phytochemicals in the selected phytonutrients using Lipinski's, Veber's and Ghose's rules. Based on our revisions for this article, all these phytonutrients have consistently shown several in vitro, in vivo, and clinical studies with great potential as preventives and therapeutics on many diseases.

Keywords: phytonutrients; phytochemicals; turmeric; garlic; cinnamon; graviola; oregano; Lipinski's Rule of 5; Veber's Rules; Ghose Filter.

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1. Introduction

For centuries, plants have been considered a significant source of medicinal nutrients and compounds. Historical findings have reported the use of plants by our ancestors to treat numerous diseases [1-3]. Consequently, it has been a quest for many individuals to search for herbal supplements and natural therapies to attend to their healthcare needs, prevent diseases, and support their nutrition. Plants produce a large variety of metabolites. Primary metabolites (i.e., innate proteins, lipids, and carbohydrates) are directly involved in the main intrinsic metabolisms as normal growth, development, and reproduction of organisms. In contrast, secondary metabolites, also known as phytochemicals, confers a selective advantage to the plant organism, despite not being involved in their main metabolic pathways [4]. These phytochemicals are classified into four main chemical groups: phenolics, alkaloids, organosulfides, and terpenes [5]. Phenolics are the biggest group subdivided into seven groups: curcuminoid, stilbenes, tannins, flavonoids, phenolics acids, lignans, and coumarins [6]. A summary of the phytonutrients' metabolite composition is shown in **Figure 1**.

Based on this definition of secondary metabolites, phytonutrients can be considered as a whole-plant extract containing one or more phytochemicals. Since one of the functions of such secondary metabolites is to protect the plant organism from pests and diseases, it is not surprising that many of them show activity against human ailments. The scientific literature contains strong evidence supporting healthy diets rich in phytonutrients as being correlated with the prevention of chronic diseases, preventive medicine being one of the most important types of health care, if not the most [7-12]. However, the ingestion of plant-derived foods, also known as "superfoods," or phytonutrients, to take advantage of its therapeutic properties is well under debate. Primarily, because of the different features affecting the looked-for properties between superfoods and extracts or phytochemicals, obtained as pure isolated compounds.

When we consume superfoods, the first feature altering their biological effect is during the food preparation, possibly inducing chemical decomposition and thermal denaturation of most metabolites, including phytochemicals [13,14]. Secondly, the different physiological barriers in the digestion process through the gastrointestinal tract determine the absorption, bioavailability, and delivery of all nutrients[15]. Multiple research groups have demonstrated the activity of the plant extract being higher when compared to the pure isolated phytochemical when orally administrated [16]. This difference is largely due to the general low bioavailability and low absorption of these isolated natural compounds, explained by their poor solubility[16-18]. To overcome this pharmacokinetic problem and study the real therapeutic potential of the pure phytochemicals, it is recommended to use other administration routes or develop improved delivery systems [19-20]. These results expose one of the most no worthy properties of the plant extracts- their synergistic interactions between the mixture of metabolites, which creates a natural micellar nanoparticle behavior [21,22].

The development of these intrinsic micelles in the extract significantly increases the successful delivery and high absorption of the phytochemical molecules [23]. On the other hand, if the phytochemical concentration in the herbal extract is extremely low, its bioactivity would be underestimated. Furthermore, the metabolites concentration, composition, and quality from batch to batch in these extracts are considerably heterogeneous [24]. These inconsistencies make extracts challenging to fulfill the high integrity and the reproducibility required to study their therapeutic activity analytically, even when people

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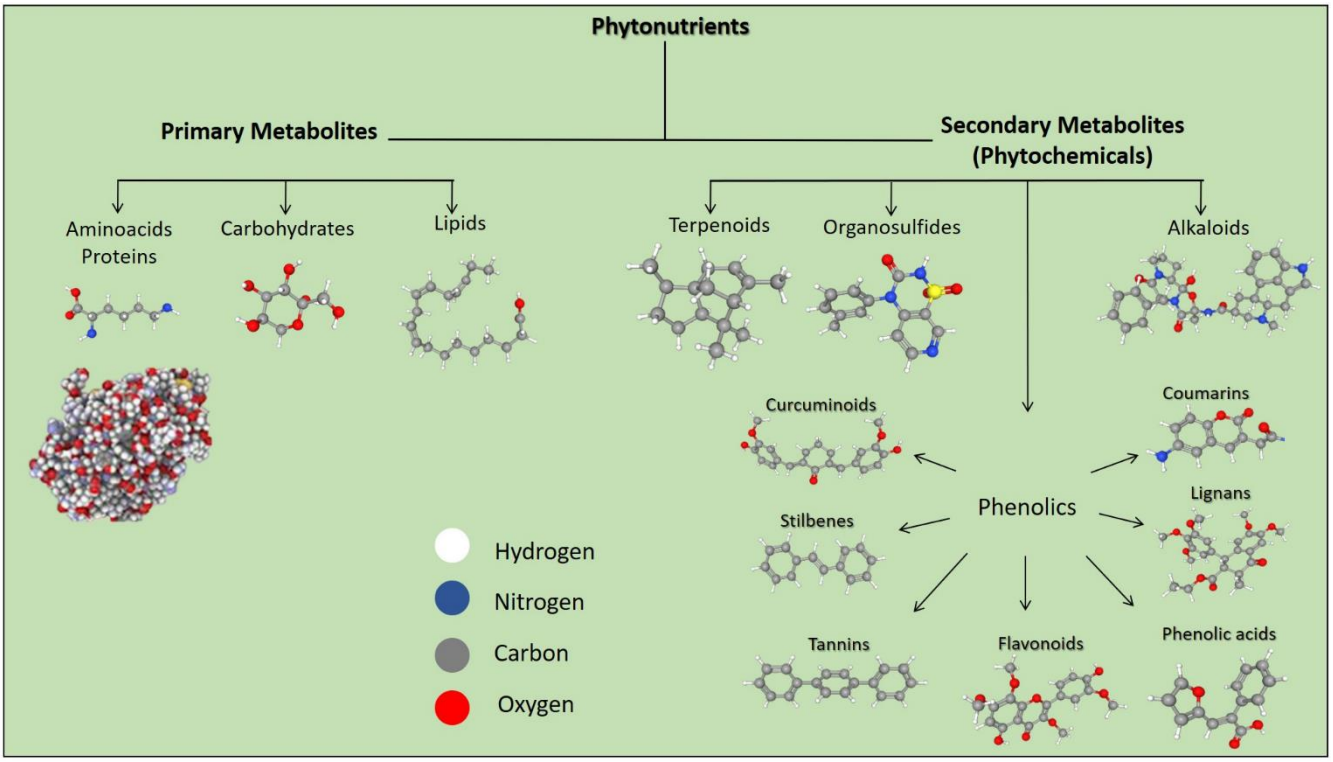

Figure 1. Phytonutrients' Composition. Plants produce primary metabolites (i.e., innate proteins, lipids, and carbohydrates) as their normal metabolic functioning and secondary metabolites (i.e., phytochemicals), primarily to protect them from predators. These phytochemicals are classified into four main chemical groups: phenolics, alkaloids, organosulfides, and terpenes. Phenolics are the biggest group subdivided into seven groups: curcuminoid, stilbenes, tannins, flavonoids, phenolics acids, lignans, and coumarins. 3D structures were visualized using PubChem [26] ball and stick model.

claim their medicinal effect [5]. Thus, for the development of new drugs, isolated active phytochemicals are preferred over crude extracts. Fortunately, basic and clinical research studies of pure phytochemicals have continued for decades and have given important therapeutic outcomes. Because of these results, almost half of the drugs available in the market are naturally derived compounds [25], showing the pertinence to our review.

Here, we aim to review studies published in the last 20 years that examine the botanical description, pharmacological, and therapeutic effect of the most popular phytonutrients, and their active phytochemicals. This review will focus on the following phytonutrients: turmeric, garlic, cinnamon, graviola, and oregano. We emphasized the biomedical areas of the anticancer, antioxidant, antiviral, anti-inflammatory, antibacterial, antifungal, and immune response presented by the mentioned phytonutrients. Besides, special attention is given to potential contraindications found while consuming these phytonutrients/phytochemicals alone or in combination with conventional medicine. After all, phytonutrients impacting the health status of individuals, in a preventive or therapeutic way, remain an attractive topic for the public looking to include food with tangible health benefits to their diets.

2. Phytonutrients

In the last 20 years, the researchers' interest in natural products has grown in search of alternatives for disease prevention and therapies. In this review, we looked for the health benefits of the selected phytonutrients demonstrated by scientific studies. Furthermore, we constructed **Table 1** to summarize our theoretical calculations of the physicochemical properties or "drug-likeness" relevant for gastrointestinal tract absorption of the main phytochemicals in the phytonutrients: turmeric, garlic, cinnamon, graviola, and oregano.

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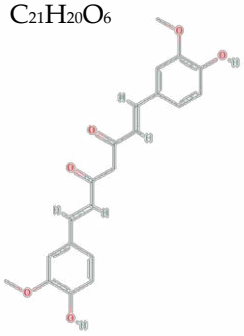
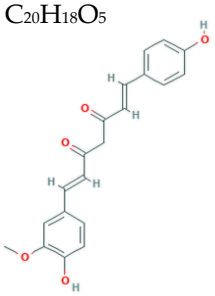
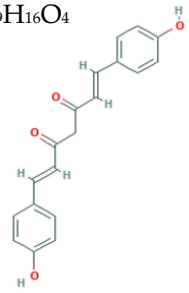
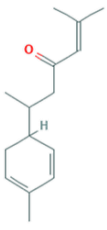
Table 1. Physicochemical properties calculations for the main phytochemicals of the selected phytonutrients.

Phytochemical compound name	Empirical formula / Structure	MW (Da)	HBA / HBD / RB	Log P	Log D	A (cm^3)	PSA ($Å^2$)	GI absorption / L-RO5, GF, and VR violations
			Turmeric					
Curcumin	$C_{21}H_{20}O_6$ 	368.4	6 / 3 / 8	2.9	2.6	106	93.1	High / 0
Demethoxycurcumin	$C_{20}H_{18}O_5$ 	338.3	5 / 2 / 7	3.2	2.6	97	83.8	High / 0
Bisdemethoxycurcumin	$C_{19}H_{16}O_4$ 	308.3	4 / 2 / 6	3.4	2.8	91	74.6	High / 0
α-Turmerone	$C_{15}H_{22}O$ 	218.3	1 / 0 / 4	4.4	4.1	69	17	High / 0
			Garlic					

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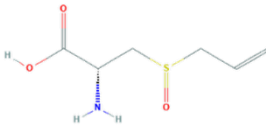
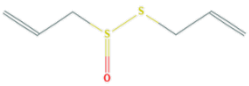
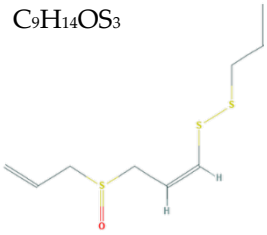
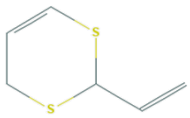
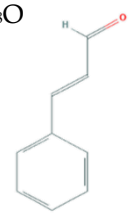
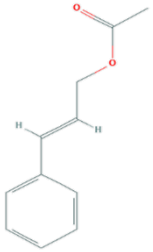
Alliin	$C_6H_{11}NO_3S$ 	177.2	4 / 3 / 5	-0.5	-3.3	44	99.6	High / 0 Negative LogD
Allicin	$C_6H_{10}OS_2$ 	162.3	1 / 0 / 5	1.2	1.4	46	61.6	Low / TNA<20
Diallylsulfide	$C_6H_{10}S$ 	114.2	0 / 0 / 4	2.6	2.9	37	25.3	Low / TNA<20 MW<160 A<40
Z-Ajoene	$C_9H_{14}OS_3$ 	234.4	1 / 0 / 8	3.1	2.8	68	86.9	High / 0
2-Vinyl-4H-1,3-dithiin	$C_6H_8S_2$ 	144.3	0 / 0 / 1	2.2	2.7	45	50.6	Low / TNA<20 MW<160
			Cinnamon					
(E)-Trans-Cinnamaldehyde	C_9H_8O 	132.2	1 / 0 / 2	2.1	1.8	42	17.1	Low / TNA<20 MW<160
(E)-Cinnamyl Acetate	$C_{11}H_{12}O_2$ 	176.2	2 / 0 / 4	2.6	2.6	53	26.3	High / 0

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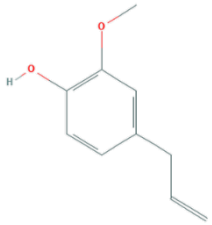
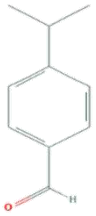
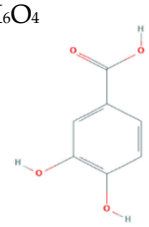
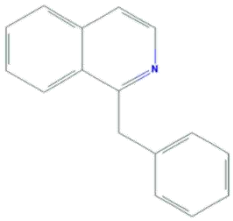
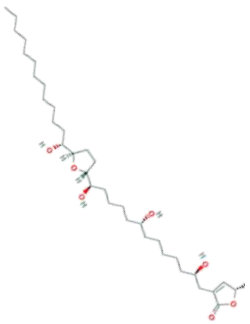
Eugenol	$C_{10}H_{12}O_2$ 	164.2	2 / 1 / 3	2.2	2.5	49	29.5	High / 0
Cuminaldehyde	$C_{10}H_{12}O$ 	148.2	1 / 0 / 2	3.0	3.1	47	17.1	Low / MW<160
Protocatechuic Acid	$C_7H_6O_4$ 	154.1	4 / 3 / 1	1.2	-1.9	37	77.8	Low / TNA<20 MW<160 A<40 Negative LogD
			Graviola					
Benzylisoquinoline	$C_{16}H_{13}N$ 	219.3	1 / 0 / 2	4.0	4.3	72	12.9	High / 0
Annonacin /Acetogenin	$C_{35}H_{64}O_7$ 	596.9	7 / 4 / 26	6.4	7.3	169	116	Low / TNA>70 MW>500 RB>10 LogP>5.6 A>130 High LogD

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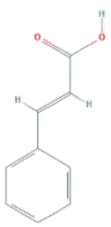
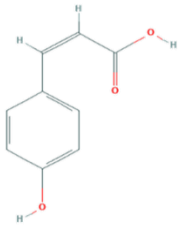
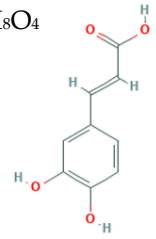
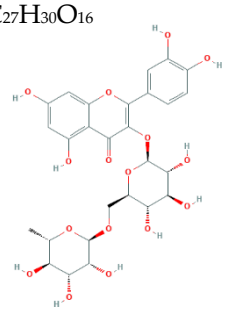
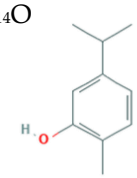
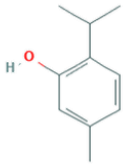
Cinnamic Acid	$C_9H_8O_2$ 	148.2	2 / 1 / 2	2.4	-0.7	44	37.3	Low / TNA<20 MW<160 Negative LogD
Coumaric Acid	$C_9H_8O_3$ 	164.2	3 / 2 / 2	2.4	-1.4	46	57.5	High / 0 Negative LogD
Caffeic Acid	$C_9H_8O_4$ 	180.2	4 / 3 / 2	1.4	-1.7	48	77.8	High / 0 Negative LogD
Rutin	$C_{27}H_{30}O_{16}$ 	610.5	16 / 10 / 6	1.8	-1.8	138	266	Low / TNA>70 MW>500 HBA>10 HBD>5 A>130 PSA>140 Negative LogD
			Oregano					
Carvacrol	$C_{10}H_{14}O$ 	150.2	1 / 1 / 1	3.3	3.1	47	20.2	Low / MW<160
Thymol	$C_{10}H_{14}O$ 	150.2	1 / 1 / 1	3.3	3.1	47	20.2	Low / MW<160

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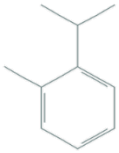
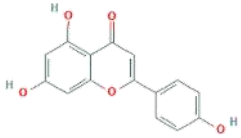
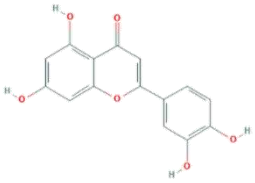
O-Cymene	$C_{10}H_{14}$ 	134.2	0 / 0 / 1	4.0	4.1	45	0	Low / MW<160
Apigenin	$C_{15}H_{10}O_5$ 	270.2	5 / 3 / 1	2.1	1.3	70	87	High / 0
Luteolin	$C_{15}H_{10}O_6$ 	286.2	6 / 4 / 1	2.4	1.1	72	107	High / 0

MW: molecular weight; S: aqueous solubility; LogP: lipophilicity; LogD: lipophilicity considering ionizable groups at pH 7.4; A: molar refractivity; HBD: Hydrogen bond donors, HBA: Hydrogen bond acceptors; RB: rotatable bonds; PSA: polar surface area; TNA: total number of atoms; L-Ro5: Lipinski's Rule of 5; GF: Ghose Filter; VR: Veber's Rules

Predicted data of Empirical formula, Structure, MW (Da), H-bond Acceptor / Donor, Log P, Log D, and A were generated using PubChem [26], ChemSpider [28], ACD/Labs Percepta Platform - PhysChem Module [29] and US Environmental Protection Agency's EPISuite™ [30].

Favorable properties or "drug-likeness" for GI tract absorption are predicted by the combination of L-RO5, GF, and VR: MW (160-500 Da); HBD ≤5; HBA ≤10; A (40-130); LogP (-0.4–5.6); RB ≤ 10: PSA<140; TNA (20-70) [27].

2.1. Turmeric

2.1.1. Botanical Description

Turmeric, also known as *Curcuma longa,* is a rhizomatous herbaceous perennial plant that belongs to the *Zingiberaceae* family (ginger family). This plant is highly branched with aromatic long leaves arranged in two rows. Turmeric flowers have colors ranging from white, green, yellowish, and purple-red [31]. *Curcuma* plants are wildly cultivated in Southeast Asia and the Indian region where is used mainly for herbal medicinal applications, dietary supplement, and cuisine purposes [32,33]. The most essential part of turmeric used as a spice and herbal supplement is the rhizome in the roots of the plant. Turmeric powder has a pungent taste and distinctive yellow/orange color due to pigments and curcuminoids phytochemicals in the rhizome [34]. Furthermore, primary metabolites (e.g., proteins and fats) and phytochemicals concentration, which dictate other physical properties and the color intensity of the turmeric powder, depending on factors like the type of soil, crop fertilizers, and pH [35].

2.1.2. Phytochemicals

Turmeric's therapeutic properties may include a wide variety of conditions found in the literature, where most of them come from the bioactive compounds in its rhizome. For years different research groups have shown that turmeric is extraordinarily rich in valuables phytochemicals with pharmacological properties including polyphenols (e.g., curcuminoids), terpenes (e.g., ar-, α- and β-turmerone, α-zingiber, and β-sesquiphellandrene), flavonoids, coumarins, saponins, tannins, and steroids [36-38]. The principal curcuminoids are curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin [32,39,40]. Curcumin is considered the major bioactive phytochemicals from turmeric and is around 5% of the rhizome. Some other bioactive compounds found in

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essential turmeric oils are aromatic-tumerones, α-santalene, and aromatic curcumene [41,42]. The biomedical uses of curcumin are limited by its short half-life, low stability, and limited bioavailability are its short half-life, low stability, and poor bioavailability [43]. However, there are different strategies under investigation to overcome these limitations, as the use of natural enhancers and the development of delivery systems to encapsulate the curcumin [44,45]. Various studies have demonstrated that primary and secondary metabolites in turmeric extracts may enhance the bioavailability of curcumin *in vivo* [43,46]. Some other phytochemicals in combination with curcumin have shown synergistic effects increasing its bioavailability, e.g., quercetin, genistein, terpineol, epigallocatechin-3-gallate, and resveratrol [47,48].

2.1.3. Biomedical effects

2.1.3.1. Anticancer

Turmeric extracts and isolated curcumin have been extensively studied for cancer applications. Since 1985, turmeric extracts have demonstrated potent cytotoxic activity against cancer *in vitro* and *in vivo* [49]. Then, it also entered clinical studies for the treatment of cancer [50]. Curcumin has been shown to diminish tumor growth effectively, prevent tumor formation, angiogenesis, migration, and invasion by modulating several cell signaling pathways related to adhesion molecules, cell survival proteins, growth factors, transcription factors, cytokines, kinases, and receptors [51]. Different studies demonstrated that curcumin downregulates cyclin D1, cyclin E and MDM2, and upregulates p21, p27, and p53 [52]. Due to the low bioavailability of pure curcumin, some researchers prefer to continue studies using turmeric extracts, co-administration with other phytochemicals, or the development of drug delivery systems. For example, Li et. al., reported that turmeric extracts (200 mg/kg) induced *in vivo* tumor growth inhibition and anti-metastatic effects using colorectal CT26, HT29, and HCT116 cancer cells [53]. Also, in combination with the phytochemical quercetin, it reveals a synergistic effect against lung, skin, colorectal, and breast cancer cells [54]. In addition, Almutairi et. al., designed the encapsulation of curcumin in a chitosan polymer nanoparticle (115 nm) to determine its anticancer activity. This curcumin-chitosan nanoparticle showed a sensitive release in more acidic pH as in cancer environment [55] are much more anticancer studies using curcumin and explaining its mechanism of action in the literature: [56-60].

2.1.3.2. Antioxidant

Curcumin is an extremely potent antioxidant by inhibiting the formation of reactive oxygen species [61]. In an *in vitro* study, Ak and Gülçin demonstrated the potent radical scavenging activity of curcumin by inhibiting >95% of lipid peroxidation [62]. Yuliani et. al., investigated the antioxidative and neuroprotective effects of curcuminoids on neurons from Sprague-Dawley rats as a potential treatment for dementia. Turmeric extract (200 mg/kg) prevents spatial memory deficits, and its effects were comparable to the standard dementia medicine, citicoline [63]. In addition, Hossen et. al., demonstrated the antioxidant properties and protective effects to hepatic organs in orally supplemented rats through a combination of curcumin (62%), flavonoids (37%), and ascorbic acid (10%). The possible mechanism of action was through antioxidant enzyme upregulation and lipid peroxidation inhibition providing protecting effects [64].

2.1.3.3. Antiviral

Several studies have demonstrated that the turmeric plant and the isolated phytochemical curcumin have exhibited activity against a wide variety of viruses due to its potential to interfere with different cellular signaling pathways, inhibiting virus proliferation and viral expression [65]. The list of viruses that turmeric demonstrated activity are Influenza A, Dengue, Viral hemorrhagic septicemia, Human immunodeficiency, Herpes simplex, Enterovirus 71, Zika, Chikungunya, Vesicular stomatitis, Human respiratory syncytial, and others [66]. In general, curcumin strongly inhibits virus proliferation and expression before it was able to infect the cells. An *in vitro* study focused on the structure-activity relationship demonstrated that double bonds in the central carbon chain

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enhanced the curcumin activity against type A influenza virus by its interaction with the receptor-binding region [67]. On the other hand, in another study, researchers claimed that the hydroxyl groups and phenyl rings of curcumin are responsible for the antiviral effect against the herpes simplex virus [68]. Curcumin showed an excellent inhibitory effect in the micromolar rage against transmissible gastroenteritis virus in cells in a dose-, temperature- and time-dependent manner [69]. In a very recent systematic review, Kunnumakkara et. al., explained the potential of curcumin and other spices against *SARS-COV-2* due to their anti-inflammatory properties to inhibit the cytokine storm [70]. These findings suggest that turmeric extracts not only could be a potential treatment but also a prevention alternative for viral infections.

2.1.3.4. Anti-inflammatory

Turmeric also exhibited potential to treat chronic pain and joint inflammation [71]. In a study using turmeric extracts in combination with Allium hookeri extracts, researchers determined that this co-treatment restored the altered skin membrane and inhibits white blood cells and monocyte proliferation in inflamed skin models [72]. Bethapudi et. al., demonstrated that oral administration of turmeric extract containing 57% of the bioactive turmerosaccharides significantly reduced pain and inflammation effects on an animal model (mimicking human osteoarthritis). This turmeric extract revealed a similar analgesic effect to tramadol on osteoarthritis pain [73]. In a recent study, Nicoliche et. al., summarized the following curcumin's mechanisms of action against the inflammatory process: inhibition of NF-KB (nuclear factor kappa B), MMP-1, 3, 8, 9, and 13 (matrix metalloproteinases), nitric oxide synthase, MAPK (mitogen-activated protein kinase), MCP (monocyte chemoattractant protein), STAT (signal transduction and activation transcription), PI3K (phosphoinositide 3-kinase), lipo-oxygenase, JAK (Janus kinase), and COX-2 (cyclo-oxygenase-2), MIP (migration inhibitory protein); also inhibition on the expression of interleukin-1, -2, -6, -8, -12 and -1β, and TNF-α (tumor necrosis factor-α); significantly improve collagen repair [74]. It is also postulated that curcumin upregulates the peroxisome proliferator-activated receptor-γ (PPAR-γ) [75].

2.1.3.5. Antibacterial

There are also reports showing the antibacterial activity of turmeric [37]. Bangun et. al., developed an alginate-based drug delivery system of turmeric extract and tested its activity against *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative). The results showed that this turmeric drug delivery system affected both strains. However, there was more prominent growth inhibition on the gram-positive bacteria than on the gram-negative [76]. Another study performed by Czernicka, and colleagues elucidated the antimicrobial potential of turmeric extract against several Gram-positive strains (one strain of *Staphylococcus epidermidis* and two strains of *Bacillus subtilis*), revealing that the different fractions of this extract can inhibit bacterial growth [37]. In the same way, Shakeri et. al., confirmed that gram-positive bacteria are more sensitive to curcumin than gram-negative bacteria due to their abundant hydrophilic lipopolysaccharide's outer membrane [77].

2.1.3.6. Antifungal

Another significant effect of turmeric is its antifungal activity. Chen et. al., showed that turmeric extracts have potent antifungal activity against 20 pathogenic fungi (e.g. *Fusarium verticillioides, Curvularia pallescens, Colletotrichum falcatum, Aspergillus niger, Aspergillus terreus, Fusarium oxysporum, Fusarium moniliforme, Fusarium graminearum, Phoma wasabiae, Alternaria alternate, Botrytis cinerea, Chaetomium olivaceum, Penicillium pallidum, Mycogone perniciosa,* and *Verticillium dahlia*) by disrupting the synthesis of the main components of the fungal cell wall and interfering the protein synthesis. From this study, phytochemicals in turmeric have better antifungal activity working in combination than individual compounds [78]. Murugesh and colleagues elucidated that turmeric extracts exhibit a potent anticandidal effect against Candida albicans on *in vitro* studies [79]. In a randomized clinical trial, researchers demonstrated that the topical administration of

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curcumin 5% ointment can significantly reduce knee pain in osteoarthritis patients [80]. This suggests the consideration of turmeric topical use as a low-cost alternative with lesser side effects considering its antifungal capacity.

2.1.3.7. Immunological

As previously described, curcumin has antioxidant and anti-inflammatory properties leading to improve immune response. In *in vivo* experiments to study Graft-versus-Host Disease (induced after bone marrow transplantation), mice were pretreated with curcumin (100 μg/mouse). These curcumin-pretreated mice showed an increase in CD4+ and CD8+ cells before the transplant preventing the disease [81] Jian et. al., studied the effects of curcumin as a dietary supplement in the male Hu sheep model, reporting changes in blood metabolites, antioxidant capacity, testicular development, and immune response. After four months of dietary supplementation, the sheep showed an improvement in the reproductive system performance [82]. *In vivo* and clinical studies indicate that curcumin can positively affect several immune cells (i.e., T lymphocyte subsets, macrophages, dendritic cells, B lymphocytes, and natural killer cells) which diminishes the severity of different autoimmune diseases [83]. Additional studies found promising results in patients with several pro-inflammatory illnesses (i.e., cardiovascular disease, renal diseases, arthritis, Crohn's disease, ulcerative colitis, irritable bowel disease, pancreatitis, peptic ulcer, gastric ulcer, oral lichen planus, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, lupus, acquired immunodeficiency syndrome, β-thalassemia, biliary dyskinesia, and Dejerine-Sottas disease) [84].

2.1.4. Contraindications

Despite the extent of evidence that reveals the beneficial effect of *Curcuma longa* extract, there might be several side effects and contraindications associated with its use. Previous studies reported that turmeric extract could increase bile secretion, trigger biliary colic to predispose patients with gallstones [85]. Besides, taking turmeric in abundance for extended periods may cause gastrointestinal ulcers [86]. In addition, it was reported that a high dose of turmeric supplementation was related to inducing atrioventricular block in patients, which disappeared once the supplementation was discontinued [86]. Furthermore, turmeric supplementation may increase the risk of bleeding if it is taken in combination with anticoagulant drugs [87]. Moreover, turmeric extract is not recommended to certain diabetic patients due to anti-hyperglycemic and insulin sensitizer effects [88]. Due to curcumin's iron chelating property, it is not recommended to a patient with iron deficiency [89].

2.2. Garlic

2.2.1. Botanical Description

Central Asia is considered the home of garlic (*Allium sativum)*, a member of the Amaryllidaceae family, even though it has been farmed for a long time worldwide. Garlic is a perennial plant that produces edible bulbs from a tall stem of 25-70 cm and can be grown in mild climates [90]. Garlic bulbs are composed of various cloves, and those who have flowers are hermaphrodites (some varieties do not produce flowers) [91]. Its leaves and cloves have been used as a spice and food additive and in traditional medicine for a long time [92]. Garlic has two major subspecies: hardneck (produce flower stalks and results in a bulb circle of 6-11 cloves) and softneck (produce no flowers and the bulb circle can result in 24 cloves [93-94]. Garlic's cultivars are divided into eight subtypes (rocambole, marble purple, purple stripes, porcelain, glazed purple stripe, Asiatic, Creole, and turban) for hardneck and into two subtypes (artichoke and silverskin) for softneck [94]. Alliums like garlic produce a pungent odor when crushed [94]. Interest in the potential benefits of this plant originates in antiquity (up to 5,000 years ago) and is one of the earliest documented examples of plants used for health maintenance and treatment of disease [95].

2.2.2. Phytochemicals

Garlic is composed of various phytoconstituents, including alkaloids, saponins, flavonoids, tannins, phenolics, terpenoids, and organosulfides [96]. In addition, garlic is considered a good source of vitamins and minerals, including vitamin B1, B6, C, manganese, copper, phosphorus, selenium, and calcium. [97]. Garlic's main phytochemicals are organosulfides (sulfur-containing compounds) including allicin, alliin, ajoenes (E-ajoene and Z-ajoene), sulfides (diallyl sulfide, diallyl disulfide, diallyl trisulfide), 2-Vinyl-4H-1,3-dithiin, and allyl methyl sulfide [98,99]. These organosulfides are produced in garlic cloves [96]. Allicin is the primary bioactive phytochemicals present in the aqueous extract of garlic and is also responsible for the characteristic odor of garlic [93]. Thus, enzyme alliinase converts allicin to alliin when the garlic cloves are sliced/crushed [100]. For this reason, several studies have shown that crushed fresh garlic can deliver most of its active phytochemical [98, 101,102]. As allicin is chemically unstable, it rearranges into the stable phytochemical ajoene (E- and Z-) [103]. Allyl sulfides are most often found in garlic oil, and vinyl-4H-1,3-dithiin is most often found in stir-fried garlic and garlic oil [104,105].

2.2.3. Biomedical effects

2.2.3.1. Anticancer

Interestingly, phytochemicals such as garlic-derived allicin have been combined with commonly used anticancer drugs to enhance the therapeutic effect of current treatments. For example, an experiment performed by Bogdan et. al., showed that a combination of the anticancer drug, 5-fluorouracil with allicin, hindered colorectal (DLD-1) and lung cancer (SK-MES-1) cell migration and proliferation *in vitro* [106]. Petrovic et. al., studied the effectiveness of intraperitoneal injections of ethanolic homemade garlic extract against an aggressive breast cancer tumor in BalB/c mice. The results showed that after 28 days of treatment, cancer growth was delayed by 30% compared with untreated mice. [107]. In another study, Tanaka et. al, led a randomized double-blinded study on 51 patients with colorectal adenomas that utilized high-aged garlic extract (2.4 ml/day) and low-aged garlic extract (0.16 ml/day) for 12 months. At least one adenoma decreased by 50% (> 6 months of uptake) in the high-aged garlic extract group, while there was no decrease in the low-aged garlic extract group [108]. Finally, a recent meta-analysis of epidemiological articles using a total of 11 clinical trials and 12,558 cases concluded that garlic intake could reduce the risk of colorectal cancer [109], coinciding with previous studies [110], while another previous meta-analysis limited to men, showed no correlation [111]. These studies show that broader investigations with increased sample size are necessary to clarify the result discrepancies from several epidemiological studies.

2.2.3.2. Antioxidant

Garlic's phytochemicals also promote an antioxidant effect. Bhatt and Patel et. al., prepared 900 mg of cooked versus raw garlic and incubated these samples with gastric enzymes. These results showed that cooked garlic lost 90% of phenolic content, leading to less antioxidant activity due to heat (evaporation of active compound) than raw garlic [112]. Lei et. al., demonstrated that the scavenging activity of black fermented garlic ethanolic extract is concentration-dependent in incubation with 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. This study also showed that this garlic extract increased the mean longevity of flies (*Drosophila melanogaster*) compared to controls [113]. In a more translational scenario, a randomized, double-blind clinical trial on seventy women with rheumatoid arthritis was made to test the effects of garlic in pain mitigation. Patients received 1000 mg of garlic for a total of 8 weeks. Results showed that pain after activities decreased in the garlic group compared to the placebo. This effect from garlic was attributed to a decrease in oxidative stress, which is a common feature in this disease [114].

2.2.3.3. Antiviral

Several studies have shown the antiviral effect of garlic. Pre-clinical studies elucidated that garlic and its organosulfides phytochemicals have great activity against several human and animal viruses by inhibiting viral RNA polymerase, reverse transcriptase, and downregulation of the extracellular-signal-regulated kinase/mitogen-activated protein

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kinase signaling pathway [115]. The variety of viruses attacked by garlic are adenovirus [116], *SARS-CoV-1* [117], dengue [118], herpes simplex [119], influenza A, B, and H1N1 [120,121], hepatitis [122], HIV [123] and rotavirus [124]. Furthermore, in a very recent study, garlic essential oil was found to be acting on the angiotensin-converting enzyme 2 (ACE2) and largely on the main protease of *SARS-CoV-2* (PDB6LU7). This activity is crucial to diminish the impact of the host receptor of *SARS-CoV-2*, and this study proposes that garlic oil active compounds can be used as a COVID-19 preventive treatment [125].

2.2.3.4. Anti-inflammatory

The anti-inflammatory effect of garlic was studied by several research groups. In an *in vitro* study, Lee and coworkers showed garlic's anti-inflammatory activity at μM concentrations. They demonstrated that garlic's organosulfides Z- and E- ajoene and analogs inhibited nitric oxide/ prostaglandins and nitric oxide synthase/ cyclooxygenase, the phosphorylation of p38 mitogen-activated protein kinases and, also the expression of the pro-inflammatory cytokines: tumor necrosis factor-α, interleukin-1β, and -6 in a lipopolysaccharide-induced macrophage cell line [126]. In a different study, Metwally et. al., investigated the anti-inflammatory effects of garlic extract and allicin *in vivo* in 140 female BALB/c mice with schistosomiasis. It was shown that garlic and allicin diminished the number of worms and the amount of proinflammatory cytokines [127]. In a double-blind clinical trial study, anti-inflammatory effects in 40 peritoneal dialysis patients were investigated by administering a garlic extract twice daily for 8 weeks. The results demonstrated that garlic diminished inflammatory markers in end-stage renal disease patients, specifically interleukin-6, C-reactive protein, and erythrocyte sedimentation rate in the treated group [128].

2.2.3.5. Antibacterial

The antibacterial effect of garlic was analyzed *in vitro* using fresh garlic juice in agar plates against *E. coli*, *P.mirabilis*, *K.pneumoniae*, *S.aereus*, and *P.aeruginosa*. The results showed a dose-dependent inhibition in all bacterial strains exposed to a garlic concentration higher than 10% [129]. In another study, two different aqueous garlic extracts (from *Allium sativum* and *Allium tuberosum)* were tested in rats infected with one penicillin-sensitive (ATCC 25923) and one methicillin-resistant (ATCC 33592) *S. aureus*. The two species of garlic were administered orally at 100 and 400 mg/kg) every 6 hrs for 24 hrs. Results showed that both garlic extracts could reduce the infection of the sensitive strain, but not against the resistant strain [130]. Thus, several *in vitro* studies demonstrated the antibacterial effect of fresh garlic extract on *E. coli, Klebsiella pneumoniae, Proteus mirabilis, P. aeruginosa,* and *S. aureus* [129]; and also, against multidrug-resistant *E. coli, P. aeruginosa, K. pneumoniae, Serratia marcescens,* and methicillin-resistant *S. aureus* [131]. In a clinical trial that involved 15 patients with *Helicobacter pylori*, the results showed that Urease Breath Test was lower in patients who took 3 g of garlic cloves twice a day, demonstrating its antimicrobial effect [132].

2.2.3.6. Antifungal

Various studies have discussed the antifungal effect of garlic. Li et. al., showed that *in vitro* experiments, garlic oil had an inhibitory effect against *Candida albicans* at a higher concentration of 0.35 μg/ml [133]. Aala et. al., performed an experiment that evaluated the structural characteristic of *Trichophyton rubrum* in response to garlic and allicin aqueous extracts. The results showed that the allicin extract was more effective in impeding the growth of fungal cells by changing fungi morphology [134]. In another *in vitro* study, results indicated that 0.125 and 0.0313 % of garlic oil had a strong antifungal activity by penetrating hyphae cells and destroy their organelles against *Penicillium funiculosum* [135].

2.2.3.7. Immunological

The immune response induced by the garlic phytochemical, allicin, was studied in female BALB/c mice. Results showed that allicin treatment reduced parasitaemias and enhanced pro-inflammatory mediators during malaria infection in a dose-dependent manner [136]. In addition, Bruck et. al., studied the immune response of allicin in induced liver

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damage BALB/c male mouse. Results showed that allicin-treated mice showed decreased levels of the pro-inflammatory tumor necrosis factor-α, aminotransferases, and improved hepatic necroinflammation [137]. A randomized, double-blind, clinical trial studied the immune and inflammatory effects of 3.6 g aged garlic extract administered daily in 51 obese adults for 6 weeks. Results showed that patients who took the extract supplementation had less pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor-α [138]. In a separate study, the immune effect of aged garlic extract supplementation was analyzed in a randomized, double-blind trial with 120 healthy participant adults to examine the proliferation of immune cells and the severity of symptoms during cold and flu season. Results showed that the garlic extract induced increased levels of NK cells, γ/δ-T cells, and reduced severity of symptoms, days, and incidence [139].

2.2.4. Contraindications

There is limited data about the safety of garlic supplements [140]. Hoshino et. al., administered 40 mg of different garlic preparations to adult dogs. Results showed significant damage caused to gastric mucosa by raw garlic powder, gastric redness caused by boiled garlic powder, and no effect by raw garlic extract [141]. In 2014, the first case of pneumonia caused by fermented black garlic was discovered in a 77-year-old female patient who came into the hospital with shortness of breath and cough after taking black garlic. Also, she tested positive via a drug-induced lymphocyte stimulation test. The patient showed health improvement when she stopped taking black garlic [142]. In addition, the first case of drug-induced liver injury by the mild periportal cholestatic reaction was reported in a 43-year-old patient who suffered from hepatopulmonary syndrome following a liver transplant by taking a high dose of *Allium sativum* as treatment. The patient's liver enzymes returned to normal after discontinuation of the treatment [140]. According to the National Institutes of Health, garlic supplements may increase the risk of bleeding. It is contraindicated to take garlic supplements if the patient takes blood anticoagulants such as warfarin or if you will undergo surgery. These supplements could interfere with the effectiveness of specific drugs used as HIV treatments. Other side effects, especially with raw garlic, could include heartburn, upset stomach, and allergic reactions [143].

2.3. Cinnamon

2.3.1. Botanical Description

Cinnamon, appreciated for centuries for its peculiar flavor and aroma, is the dried inner bark of *Cinnamomum verum* (syn. *C. zeylanicum* Blume), an evergreen tree native of Sri Lanka and India. This *C. verum* is also commonly called as "true" cinnamon or Ceylon cinnamon. The *Cinnamomum* genus, which the cinnamons are part of, belongs to the laurel family (*Lauraceae*), and it includes about 250 evergreen aromatic trees and shrubs [144]. Most of the spice sold as cinnamon in the United States, however, comes from another cinnamon species, *Cinnamonum cassia,* also called Chinese cinnamon, because of its geographical origin in the mountains of China [145]. The botanical features of *C. verum* are summarized as trees (up to 50 ft) with long lance-shaped leaves, small yellow flowers organized in a cluster, and ovoid-shaped fruits. The botanical features of *C. cassia* are summarized as trees (up to 65 ft) with thin lance-shaped leaves, white flowers axial inflorescences, and globose drupe fruits [146].

2.3.2. Phytochemicals

Qualitative phytochemical screening of a methanolic extract from the bark of *C. verum* showed the presence of all four categories of secondary metabolites. It has also been shown that the phytoprofiles of the cinnamon extracts depends on the botanical part of the tree used for extraction; while essential oils from the *C. verum* bark mainly contain cinnamaldehyde and linalool, the flower and fruit extracts are enriched in (E)-cinnamyl acetate, and eugenol is the main compound of leaf extracts [147,148]. The bark of the cinnamon tree has also been reported to contain coumarin, a benzenoid lactone. *C. cassia* is particularly rich in coumarin (3462.0 mg/kg in *C. cassia* vs 12.3 to 143.0 mg/kg for *C. verum*)

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[149]. The solvent and temperature should also be carefully selected according to the molecule one wishes to extract, for example, water is a better solvent for extracting the phenols from *C. verum* than polar organic solvents at 200°C [150]. For Klejdus et. al., however, the factor for efficiently extracting mainly depends on the state of the destruction of the cinnamon cell structures during the extraction protocol [151].

2.3.3. Biomedical effects

2.3.3.1. Anticancer

In vitro and *in vivo* studies by Yang et.al., show that the essential oil of cinnamon extracted from the bark of *C. cassia* significantly inhibits the growth of head & neck cancer cells and tumors in mice. The antitumor activity was believed to be mediated by the trans-cinnamaldehyde acting as a competitive inhibitor of the epidermal growth factor receptor (EGFR). This kinase is often mutated and overexpressed in many tumors and regulates key cancer metabolic pathways such as proliferation, apoptosis, angiogenesis, and tumor invasiveness [152]. Similarly, Koppikara et. al., reported that aqueous bark extract from *C. cassia* inhibits the growth of cervical carcinoma *cells* in a dose-dependent manner (IC_{50} = 80μg/mL) by apoptosis and loss of mitochondrial membrane potential. The treated cells exhibited reduced migration potential by the downregulation matrix metallopeptidase 2 (MMP-2) and the EGFR. [153]. Furthermore, Perng et. al, demonstrated that *C. verum* component 2-methoxy-cinnamaldehyde had an antiproliferative effect on human hepatic adenocarcinoma both *in vitro* (IC_{50}= 25.72 μM for 48h) and *in vivo* (10-20 mg/kg/d administration of 2-methoxy-cinnamaldehyde). The targeted metabolisms determined by this group were like the previous studies (i.e., mitochondrial apoptotic pathway), and activation of caspase-3 and -9, a sub-G1 phase cell cycle arrest and downregulation of nuclear factor-Kβ (NF-Kβ) [154].

2.3.3.2. Antioxidant

A study on the peripheral blood mononuclear cells of rheumatoid arthritis patients showed that cinnamaldehyde and eugenol significantly reduced the levels of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6. Also, these patients showed enhanced activity of the enzymes: superoxide dismutase, glutathione peroxidase, and catalase, suggesting an antioxidant effect. [155]. In the same way, Davaatseren et. al., demonstrated that trans-cinnamaldehyde diminish the production of nitric oxide and reactive oxygen species in macrophages [156]. Furthermore, cinnamon capsules were orally administered for 12 weeks in a small controlled clinical trial to women with polycystic ovary syndrome. This study demonstrated that cinnamon improved the antioxidant status and lipid profile of these patients by decreasing serum levels of malondialdehyde (derived from lipid peroxidation), total cholesterol, triacylglycerol, and increasing high-density lipoproteins. [157].

2.3.3.3. Antiviral

In vitro studies concluded that essential oil extracts from the leaves of *C. verum* extract had an antiviral effect in cells infected with the Influenza type A (H1N1) [158]. Similarly, a study by Moshaverinia suggests that a hydroalcoholic extract of *C. verum* at 1 mg/mL significantly reduces the viral titer of the human herpes simplex virus type 1 -infected cells [159]. Furthermore, in silico studies by Kulkarni et. al., suggest that cinnamaldehyde possesses a strong affinity to the S1 receptor binding domain of the spike (S) glycoprotein of the severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2).* Cinnamaldehyde could therefore be an efficient pharmacological agent to inhibit the entry of the virus into the host cells [160].

2.3.3.4. Anti-inflammatory

A study conducted in an *in vitro* human skin model for chronic inflammation and fibrosis suggests that a concentration of 0.0012% (v:v) significantly inhibits the expression of genes involved in the inflammation and immune DNA damage responses. The authors attributed the effect to the cinnamaldehyde, and cinnamyl acetate, the two main chemical

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compounds present in the extract [161]. Likewise, Gunawardena et. al., have demonstrated that *C. verum* and *C. cassia* extracts inhibited the release of pro-inflammatory nitric oxide molecule and tumor necrosis factor protein in activated macrophages. From these results, the ethanolic extract from *C. verum* showed more activity than the aqueous extract (IC_{50} = 36.4 and 122 μg/ml, respectively). The phytochemicals with more anti-inflammatory effects were E-cinnamaldehyde and o-methoxycinnamaldehyde [161]. Furthermore, in an *in vivo* study, 4.5 ml/kg of the ethanolic cinnamon extract was orally administered to a mouse model for colitis. The treated mice exhibited significantly enhanced resorption of their colon fibrotic tissues and reduction of the fibrotic score associated with a decrease in the expression of extracellular matrix proteinases [162].

2.3.3.5. Antibacterial

Ahmed et. al., showed that aqueous, methanolic, and acetone extracts from C. verum bark exerted significant antibacterial effects on *S. aureus*, *P. aeruginosa*, and *E. coli.* The inhibitory effect of the extracts was believed to be mediated by cinnamaldehyde [163]. Furthermore, an *in vivo* study conducted on aquatic pathogens in zebrafish, Faikoh et. al., concluded significant antimicrobial effects of liposome-encapsulated cinnamaldehyde in fish-infected by *A. hydrophilia*, *V. vulnificus*, S. *agalactiae*, *V. parahaemolyticus*, and *V. alginolyticus.* The antimicrobial activity of the drug was associated with a decrease in the expression of the pro-inflammatory interleukin -1β, -6, -15 and with an increase of the interleukin-10 [164].

2.3.3.6. Antifungal

In a 2019 study, Kowalska et. al., demonstrated the antifungal properties of 1 % (v/w) aqueous *C. verum* bark after a 6-day treatment against *Botrytis cinerea*, the mycelium responsible for the grey mold disease in tomato plants [165]. Furthermore, cinnamon seems to inhibit the growth of the microorganisms of the *Candida* family, which are responsible for most of the fungal diseases in humans. In a clinical trial study, Wang et. al., showed that an oil extract from *C. verum* significantly inhibited the growth of three species of *C. albicans* (IC= 0.064 mg/mL), *C. tropicalis* (IC= 0.129 mg/mL), and *C. krusei* (IC= 0.129 mg/mL) [166]. Additionally, a study conducted on guinea pigs suggests that topical treatments with methanolic extracts of *C. verum* inhibit the growth of *M. canis* and *T. mentagrophytes*, two fungi involved in skin infections in animals and humans [167].

2.3.3.7. Immunological

Several studies have concluded that the phytochemicals present in cinnamon extracts inhibit the immune response associated with allergies. Mast cells, key effectors in allergic diseases, are considered promising therapeutic targets. Hagenlocher et. al., have shown that cinnamon extracts decrease the release and expression of pro-inflammatory mast cell mediators such as β-hexosaminidase, cytokines CXCL8, and chemokine ligand 2, 3, and 4. From this study, the anti-allergic properties are believed to be mediated by cinnamaldehyde [168]. Similar results have been found in human and murine models for allergic inflammation. Cinnamon extracts significantly inhibited the allergen-specific T cell proliferation as well as TH1 and TH2 cytokine production [169].

2.3.4. Contraindications

While cinnamon possesses a large specter of medicinal properties, its regular consumption can also lead to adverse health effects. Ingestion of a big spoon of dry cinnamon spice may lead to scarring to airways, or even pneumonia [170]. Due to its apoptotic effect of cinnamaldehyde on B and T-cells, the consumption of cinnamon is contraindicated in patients under an immunotherapy treatment [171]. The consumption of cinnamon should be avoided during pregnancy since cinnamon can induce contractions and may lead to premature labor [172]. Importantly, studies conducted both *in vitro* and *in vivo* suggest that coumarin, abundant in *C. cassia*, is a potential carcinogen to individuals with mutations of the Cytochrome P450 2A6 [173].

2.4. Graviola

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2.4.1. Botanical Description

A member of the *Annonaceae*/ Custard-apple family, *Annona muricata*, commonly known as soursop, graviola, paw-paw, or "guanabana" is a tree native to Central America and West Indies that is abundant at altitudes lower than 900 m above sea level. It is nowadays cultivated in tropical and subtropical climates in countries such as Angola, Brazil, Colombia, Costa Rica, Puerto Rico, India, and Venezuela [174]. The graviola tree is mainly appreciated for its edible fruit. Still, its parts (leaves, fruit, bark, root, etc.) have been commonly used in traditional pharmacopeia in the form of macerations, decoction, or as a topical medication [175,176]. While the graviola tree can grow in a large variety of soils, it prefers deep soils with good oxygenation [174]. Botanically speaking, its leaves are large and obovate to elliptically shaped, are green on top, and paler on under top with short petioles and a pungent smell. The tree produces yellow-greenish flowers and lags about two years in producing heart-shaped fruits. It usually bears fruits yearly from that point on and can produce up to ten fruits from its fifth year [177].

2.4.2. Phytochemicals

More than two hundred (>200) bioactive compounds have been isolated from the leaves, seeds, root, bark, fruit, and fruit peel of the graviola tree [176]. Most frequently identified are alkaloids, phenolics, and terpenoids [178,179]. Acetogenins are considered the main bioactive compound in the *Annonaceae* family, with over 120 acetogenins identified from the root, leaves, stems, fruit pulp, and the seed of the family members [180,181]. Acetogenins are a special class of secondary metabolites that could be considered part of the phenolics integrating polyketides and polyethers found exclusively in the plants of the *Annonaceae* family [182]. The structure of acetogenins is composed of a long carbon chain (35-38 carbons) as a fatty acid derivative. graviola leaves contain key medically relevant polyphenolics compounds, including quercetin, rutin, and gallic acid [183-185]. The leaves of graviola also contain close to eighty (80) essential oils, among which are bioactive sesquiterpenes, and compounds such as potassium, calcium, zinc, phosphorus, magnesium, carbohydrates, vitamin A, B, and C, phytosterol, and calcium oxalate [186,187].

2.4.3. Biomedical effects

2.4.3.1. Anticancer

Graviola anticancer activity has been extensively studied, and the cytotoxicity of graviola has been reported for several cancer types e.g., breast, colorectal, skin, head and neck, lung, liver, pancreatic, prostate cancer, and leukemia [174, 188-190]. Most of the antiproliferative properties of the extracts are believed to be mediated by the graviola acetogenins. The acetogenins exert an inhibitory activity on the NADPH mitochondrial complex 1, a component of the energy transport chain, which is crucial to the synthesis of high quantities of ATP in cancer cells. [189,191,192]. Acetogenins have also been shown to target several critical cancer metabolic pathways by inhibiting the Na^+/K^+ ATPase pump and the hypoxic and glycolytic pathways, inducing apoptosis and cell cycle arrest [192-194].

2.4.3.2. Antioxidant

Studies conducted *in vitro* and *in vivo* suggest that graviola contains antioxidant compounds that act as free-radical scavengers and increase the activity of the antioxidant enzymes superoxide dismutase and catalase and downregulate the function of mitochondrial NADPH oxidase complex I, [195-197]. The leaf and the fruit pulp of graviola are the parts of the tree with the highest antioxidant properties [178]. The antioxidant activity of graviola is believed to be mediated by the phenolic phytochemicals: quercetin, gallic acid, and graviola leaf polysaccharides [198,199].

2.4.3.3. Antiviral

It has been suggested that the phytochemicals polyphenolics in graviola exert some antiviral activity against RNA and DNA viruses [185,200]. A study by Wahab et. al., showed that pretreating monkey kidney epithelial cells with a graviola leaf extract 24h-prior to infecting them with the dengue virus serotype 2, inhibited the virus replication.

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The treatment also increased the survival of the dengue-infected cells [201]. A recent clinical study conducted by Le Donne et. al., investigated the antiviral properties of graviola on human papillomavirus (HPV)-infected patients who were supplemented with ellagic acid and graviola extract twice a day for six months. Results showed a 74% HPV clearance in treated patients compared to the 25% clearance for the placebo group [202]. Furthermore, recent in silico studies suggest that rutin, a phytonutrient abundant in graviola, could act as strong ligands and inhibit the function of proteins of the *SARS-CoV* and *SARS-CoV-2* virus, thus suggesting potential therapeutic benefits against the COVID-19 infection [203,204].

2.4.3.4. Anti-inflammatory

The anti-inflammatory properties of graviola have been extensively studied *in vitro* and *in vivo* [205]. Cercato et. al., reported that a topical application of a graviola leaf extract (0.3, 1, or 3 mg/ear) significantly reduced ear edema and myeloperoxidase activity in Swiss mice with 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear inflammation. The authors were also able to show that the anti-inflammatory effect of the extract was associated with a reduction of the total amount of hydroperoxides, and with modulation of catalase antioxidant activity [206]. While studying the anti-inflammatory response in Lipopolysaccharide (LPS)-stimulated murine macrophage cell line RAW264.7 treated with graviola ethanolic leaf extracts, Laksmitawati et. al., reported a downregulation in the pro-inflammatory protein markers tumor necrosis factor-alpha (TNF-α), interleukin-1β, interleukin-6 in the treated macrophages cells compared to untreated controls [207]. Furthermore, graviola aqueous extract suppresses nitric oxide production [208]. Similarly, an *in vivo* study conducted in rodents by Ishola et. al., showed that the administration of a lyophilized graviola fruit extract inhibits the activity of the pro-inflammatory biomarkers cyclooxygenase (COX)-1 and COX-2 in a dose-dependent manner [209].

2.4.3.5. Antibacterial

Graviola leaf extracts have been shown to exert an *in vitro* antibacterial activity against oral pathogenic strains such as *S. mutants, S. mitis, P. gingivalis, P. intermedia, P. intermedia, and C. albicans* [210,211]. An *in vivo* study conducted in albino rats demonstrated the efficiency of graviola unripe fruit extracts to inhibit the growth of *S. typhi* [212]. Furthermore, aqueous leaf extract and fruit-skin ethanolic graviola extracts showed a strong antibacterial effect against *K. pneumoniae, S. aureus,* and *P. aeruginosa*, bacteria, the pathogens responsible for respiratory infections in the Human Immunodeficiency Virus (HIV/AIDS) patients [213].

2.4.3.6. Antifungal

We did not find studies testing the antifungal activity of any graviola extract. However, we found studies evaluating this property in some of graviola's phytochemicals. In 2017 a research group found that gallic acid has *in vitro* antifungal activity against dermatophyte strains (between 43.75 and 83.33 μg/mL), and Candida strains (*C. albicans* IC= 12.5 μg/mL, and *Trichophyton rubrum* IC= 43.75 μg/mL) by inhibiting the ergosterol synthesis. They also confirmed this activity *in vivo* studies administrating 80 mg/kg d of gallic acid [214]. In another study, researchers found that quercetin induces apoptosis in *Candida albicans* through mitochondrial dysfunction by increasing intracellular magnesium [215].

2.4.3.7. Immunological

Several studies have reported that graviola possesses immunomodulatory properties. For example, a study conducted in rodents by Umayra et. al., shows that administration of an ethanolic graviola leaf extract triggers a boost in the immunological response through the activation of phagocytic cells [216]. Furthermore, an immune-enhancing activity of graviola leaf extracts has been observed in RAW 264.7 macrophage cells *in vitro*, a phenomenon which is believed to be mediated by the activation of the mitogen-activated protein kinase (MAPK) pathways [217].

2.4.4. Contraindications

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In vitro and *in vivo* studies suggest that the acetogenins and alkaloids present in the graviola fruit could be toxic to neurons [188]. While patients with neurological ailments should avoid consuming graviola altogether, the benefits/contraindication of graviola should be carefully evaluated on a case-by-case basis.

2.5. Oregano

2.5.1. Botanical Description

The term oregano refers to a group of several plant genera, including *Thymbra*, *Thymus*, *Coridothymus*, *Satureja*, and *Origanum*, containing a high amount of the phytochemical carvacrol in their essential oils. The genus *Origanum* consists of 43 species. *Origanum vulgare (O. vulgare)*, commonly named "oregano", is the name of the aromatic plant used as a condiment herb in Mediterranean cuisine [218-220]. *O. vulgare* size is usually 20-80 cm, its 1-4 cm leaves are dark green, with 2 mm bell-shaped calyx purple flowers arranged in erect spikes [221-223]. Like other aromatic plants, the oregano plant produces essential oils as secondary metabolites in response to various infectious agents, UV light, and even oxidative stress. Oregano essential oils (OEOs) are usually extracted from the plant leaves and flowering tops. OEOs are famous for their medicinal value and are traditionally used in Turkey to cure diseases like cough, chronic cold, wounds, gastrointestinal disorders, and skin problems in humans and domestic animals [224].

2.5.2. Phytochemicals

The main bioactive compounds present in the OEOs are the aromatic oxygenated monoterpene thymol (5-methyl-2-(1-methylethyl) phenol) and its constitutive isomer carvacrol (5-isopropyl-2-methylphenol, 2-p-cymenol). The ratio of thymol/carvacrol varies according to the oregano plant's geographical location [225]. Both compounds are lipophilic, volatile, highly soluble in ethanol, and possess low densities [224, 226-228]. Other bioactive oregano phytochemicals include o-cymene (2-Isopropyltoluene), apigenin (4′,5,7-trihydroxyflavone), and luteolin (7,3',4',5-tetrahydroxyflavone) [229,230]. Due to their general low toxicities, the two main chemicals of *O. vulgare*, thymol and carvacrol have been approved as food additives by the Food and Drug Administration (FDA) [231].

2.5.3. Biomedical effects

2.5.3.1. Anticancer

The antiproliferative/anticancer properties of oregano have been documented *in vitro* and animal models for cancers. A recent study by Spyridopoulou et. al., showed that OEO exerts dose-dependent cytotoxicity against breast cancer (MCF-7), colon cancer cells (HT-29), melanoma (A375), and hepatocellular carcinoma (HepG2) cells, with respective IC_{50} values of 0.35, 0.35, 8.90, and 10.0 mg/mL. The authors also showed that the treatment of HT-29 cells with 50 mg/mL of OEO correlated with an attenuated migration and an induced apoptosis-related morphological change in HT-29 cells. Furthermore, the oral administration of OEO for 13 days (0.370 g/kg b.w/day) proved to inhibit the growth of CT26 colon tumors *in vivo* in BALB/c mice [232]. Another study by Coccimiglio reports that an ethanolic leaf extract of *O. vulgare* promotes the death of A549 human lung carcinoma in a dose-dependent manner (IC_{50}= 14.0 µg/mL) [233]. The antiproliferative properties of oregano are believed to be mediated by thymol and carvacrol, which possess antioxidant characteristics while being non-mutagenic to cells [233-235]. The anticancer properties of thymol were evidenced in in-vitro and *in vivo* models for colorectal cancers [236,237]. One astonishing property of carvacrol is its potential to specifically target cancer cells while being less toxic to normal cells [238]. Furthermore, carvacrol seems to exert a modulatory effect on the toxicity of cisplatin *in vitro*, a property that could be exploited for reducing the side-effects associated with classical cisplatin-based antitumor treatments [235].

2.5.3.2. Antioxidant

An *in vitro* study by Gavaric et. al., showed that OEO possessed a strong antioxidant activity (IC_{50}= 0.2 µg/mL). While thymol and carvacrol were the components accounting

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for the antioxidant properties of oregano, the antioxidant activities of the two compounds were much inferior to the one observed for the whole extract with (IC_{50} = 70-80 mg/mL for thymol and carvacrol). The authors concluded that thymol and carvacrol, and other extract phytocompounds acted in synergy to promote the scavenging of free radicals [239]. According to a study conducted on the human colon carcinoma intestinal Caco-2 cell line, thymol, carvacrol, and their mixture seem to exhibit double-edged anti or prooxidant effects, depending on the concentration at which they are administered (pro-oxidants at sub-cytotoxic concentrations vs. antioxidants at higher concentrations) [240].

2.5.3.3. Antiviral

An *in vitro* study conducted on simian Vero cell line CCL-81 showed that thymol, carvacrol, and p-cymene (all major components of oregano oils) possess antiviral properties against the human herpes simplex virus type 1 with respective IC_{50} values of 0.002%, 0.037%, and >0.1%. The antiviral properties of the three compounds are believed to be correlated to their ability to interfere with the viral membrane fusion mechanism during the adsorption phase of the virus [241]. Furthermore, an *in vitro* study by Sánchez & Aznar have reported a dose-dependent titer inhibition of the feline calicivirus and the murine norovirus by thymol, in the 1-2% (v:v) range concentrations [242].

2.5.3.4. Anti-inflammatory

OEOs possess a strong anti-inflammatory activity, a property that is believed to be mediated by its main active compounds: thymol and carvacrol. The impact of the OEOs on 17 protein biomarkers closely related to the inflammatory response. The results show dose-dependent inhibition of the expression of all the proinflammatory biomarkers. Carvacrol was reported to be the main constituent of the essential oil, making up 78% of the total composition of its weight [243]. The anti-inflammatory activity of thymol was also reported *in vivo* in BALB/c mice affected by LPS-induced endometritis [244].

2.5.3.5. Antibacterial

Thymol and carvacrol have been shown to exert antibacterial activities against gram-positive and gram-negative bacteria [245]. In studies using thymol concentrations ranging from 26.5-52.9 mg/cm^2 showed strong inhibitory activity against the *S. aureus, B. subtilis, E. coli,* and *Salmonella enteritidis* [246]. Studies performed by Du et. al., showed the following results: strong antibacterial activity of the OEOs, thymol, and carvacrol against *E. coli, C. perfringens*, and Salmonella strains. They also performed *in vivo* studies in 448 male broiler chicks by oral gavage using OEO. They found that OEO alleviated intestinal lesions and decreased *E. coli* populations [247]. In another study, oregano oil showed great antibacterial activity against the following multidrug-resistant bacteria: three *Acinetobacter baumannii*, three *Pseudomonas aeruginosa*, and four methicillin-resistant *Staphylococcus aureus* with inhibitory concentrations ranging from 0.08-0.64 mg/ml [248]. Another *in vitro* study shows that the use of OEO and carvacrol could curve Group A *streptococci* erythromycin-resistant bacterial infections [249].

2.5.3.6. Antifungal

The *in vitro* antifungal properties of OEO, thymol, and carvacrol in the 40-350 mg/mL ranges, have been reported in several studies against plant pathogenic fungi *Colletotrichum acutatum* and *Botryodiplodia theobromae* [250], against *Penicillium digitatum* and *Penicillium italicum* [251], against food-relevant fungi *Cladosporium spp.* and *Aspergillus spp.* [252], against longan pathogens, *Lasiodiplodia spp., Phomopsis spp., Pestalotiopsis spp.* and *Geotrichum candidum* [253], and against Fusarium verticillioides and Rhizopus stolonifera [254]. In a very recent study, Serna-Escolano et. al., determined that thymol and carvacrol encapsulated in the polymer 2-hydroxypropyl-beta-cyclodextrin were highly effective in reducing the growth rate of *Geotrichum citri-aurantii* (which causes sour rot in citrus fruits). Furthermore, an *in vivo* study conducted in *Caenorhabditis elegans* suggests that thymol possesses antifungal activity against *Candida albicans*, the most prevalent cause of fungal infections in humans [255].

2.5.3.7. Immunological

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De Santis et. al., have studied the immunomodulatory effects of several 50% (v/v) hydroalcoholic *O. vulgare* extracts on human-derived dendritic cells type-1 and type-2 macrophages infected with *M. bovis* Bacille Calmette-Guérin. The authors showed that the hydroalcoholic extract stimulated the anti-mycobacterial innate immunity and limited the inflammatory response in all the tested cell types [256]. On the contrary, Gholijani et. al., showed that intraperitoneal injections of 80 mg/kg of thymol or carvacrol in BALB/c mice trigger an immunosuppressive response, a property that could be exploited for treating autoimmune diseases [257].

2.5.4. Contraindications

As detailed in this review, *O. vulgare* offers a large spectrum of health benefits. Caution should be taken, however, with its medical use due to some negative health effects of its most abundant chemical constituents: thymol and carvacrol. Tisserand et. al., have shown that thymol is an irritant to the mucosal membrane [258]. Furthermore, despite being non-toxic at low to moderate doses, thymol and carvacrol have shown to induce dose-dependent structural chromosomal aberrations in *Rattus norvegicus*, when administered at doses of 40 mg/kg and up [259].

3. Discussion

Phytochemicals are vital cofactors with powerful effects on the body, helping it regain functionality. As shown in this review, even though phytochemicals may have different mechanisms of action and different levels of effectiveness in the body, there are overlapping aspects such as antioxidant, anti-inflammatory, and metabolic corrective effects that produce a variety of positive physiological repercussions that favor the healthy state. The physiologic modulation induced by these phytonutrients and their phytochemicals produces functional changes that support repair mechanisms necessary to achieve the homeostasis or balance known as health.

The physicochemical properties calculated for the main phytochemicals in the phytonutrients studied in this review are based on the combination of Lipinski's, Ghose's, and Veber's rules (L-Ro5, GF, VR), described as an approximation for the pharmacokinetics of a molecule in the body [27]. Thus, a molecule whose structure falls out of the range of these rules is predicted to have poor absorption or permeation through the gastrointestinal system and low systemic bioavailability.

From the evaluation of 25 phytochemicals through the mentioned parameters (**Table 1**), 23 of them fulfill the requirements of L-Ro5 (HBD ≤ 5, HBA ≤ 10, MW ≤ 500, logP ≤ 5) and VR (RB ≤ 10, PSA ≤ 140), while 2 (annonacin /acetogenin and rutin from graviola) violated more than one parameter. Per GF, the compounds should meet the following: MW (160 – 480), logP (-0.4–5.6), A (40-130), TNA (20-70). Accordingly, 13 phytochemicals (curcumin, demethoxycurcumin, bisdemethoxycurcumin, and α-turmerone from turmeric; alliin, allicin, and z-ajoene from garlic; (E)-cinnamyl acetate and eugenol from cinnamon; benzylisoquinoline, coumaric acid and caffeic acid from graviola; apigenin and luteolin from oregano) comply with Ghose's rules.

Considering GI tract absorption (**Figure 2a**) 54% of all phytochemicals studied in this review (curcumin, demethoxycurcumin, bisdemethoxycurcumin, α-turmerone, alliin, z-ajoene, (E)-cinnamyl acetate, eugenol, coumaric acid, caffeic acid, apigenin, and luteolin) met all rules and thus, have a higher probability of being highly absorbed. Based on L-

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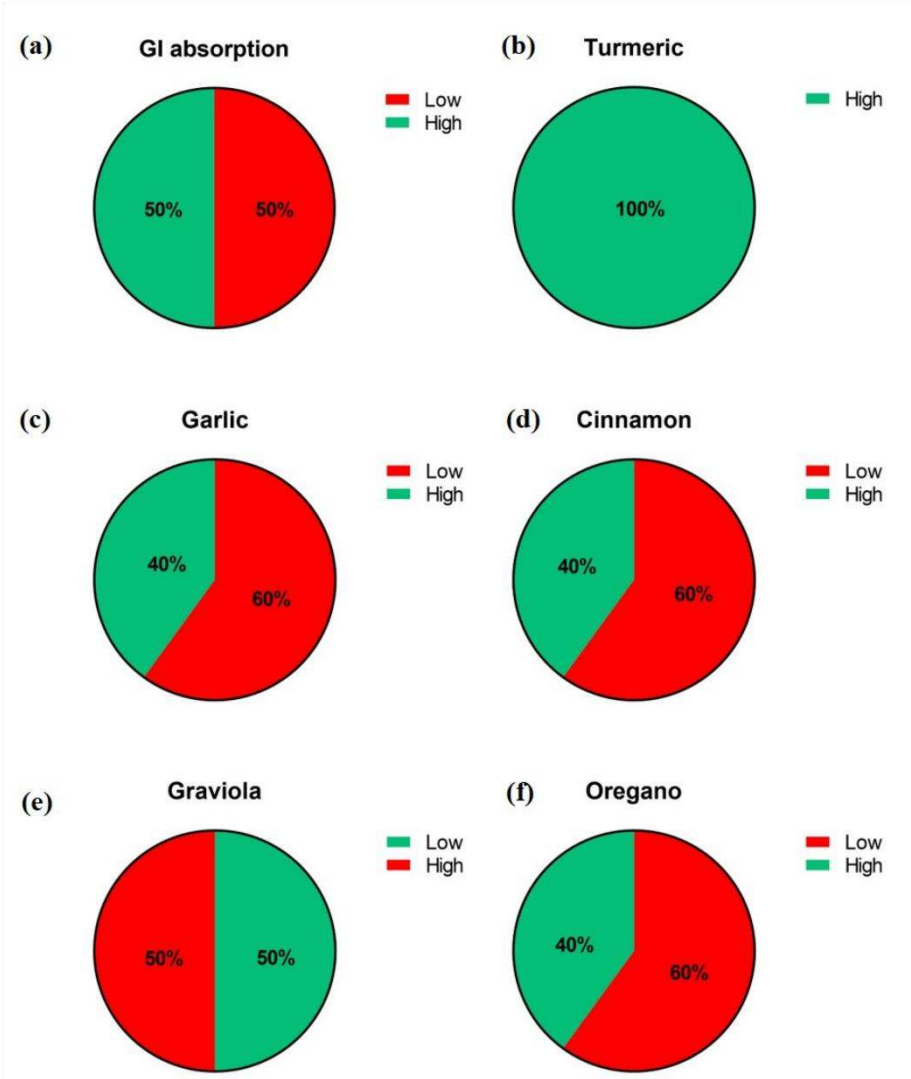

Figure 2. GI absorption for described phytochemical compounds. (a) Percent (%) of phytochemicals of all selected phytonutrients with high or low probability for GI absorption. Percent (%) of (b) Turmeric, (c) Garlic, (d) Cinnamon, (e) Graviola, and (f) Oregano phytochemicals with high or low probability for GI absorption.

Ro5, GF, and VR, all described turmeric's phytochemicals belong to highly absorbed compounds (100%) compared to garlic, cinnamon, and oregano (40%) (**Figures 2b, 2c, 2d, 2f**) and graviola (50%) (**Figure 2e**).

Graviola's phytochemicals, annonacin /acetogenin, and rutin violate the majority of the "drug-likeness" rules. For example, annonacin /acetogenin complies with only 50% L-Ro5 and VR and violates 100% of GF. For rutin, the compliance for L-Ro5 was 25%, for GF was 25% and for VR was 50%. Thus, it is predicted that annonacin /acetogenin and rutin have the lowest probability of being absorbed in the GI.

Other researchers have proposed that the lipophilicity considering the ionizable groups at pH 7.4 (LogD) is much more important for physiological absorption or permeation [260]. Thus, compounds that fall below 1 and above 5 for LogD are less likely to be absorbed. Based on this, alliin from garlic; protocatechuic acid from cinnamon; annonacin /acetogenin, cinnamic acid, coumaric acid, caffeic acid, and rutin from graviola fall out this LogD range.

However, the predictions of these rules are also based on molecules passively transported into the cells. This means that L-Ro5, GF, and VR do not take into consideration actively transported substrates by biological transporters (e.g., cellular receptors or channels) [261]. On the contrary, we understand that a large group of therapeutic compounds is actively transported in the organism, especially plant-based compounds. Due to this,

other studies have shown that most of the violators of these rules are natural products [262]

4. Conclusions

All the phytonutrients mentioned in this review article, when used properly, have demonstrated a large variety of health benefits. Yet, a medical evaluation is needed before any decision is made on utilizing phytonutrients and phytochemicals regularly or in combination with another medical pharmacological treatment.

5. Patents

N/A

Supplementary Materials: N/A

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Appendix A

N/A

Appendix B

N/A

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