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Abstract

Spices are not only just herbs used in culinary for improving the taste of dishes. They are also sources of a numerous bioactive compounds significantly beneficial for health. They have been used since ancient times because of their antimicrobial, anti-inflammatory and carminative properties. Several scientific studies have suggested their protective role against chronic diseases. In fact, their active compounds may help in arthritis, neurodegenerative disorders (Alzheimer's, Parkinson, Huntington's disease, amyotrophic lateral sclerosis, etc.), diabetes, sore muscles, gastrointestinal problems and many more. In the present study, possible roles of spices and their active components, in chronic diseases (cancer, arthritis, cardiovascular diseases, etc.) along with their mechanism of action have been reviewed.

Keywords: spices, natural products, chronic diseases, neurodegenerative diseases

1. Introduction

Chronic diseases, such as diabetes, inflammatory cancer, pulmonary, cardiovascular and neurodegenerative disease, are the main cause of human death all around the world. Most of these risk factors are closely connected to chronic inflammation, which leads to the development of various diseases. One of the main causes of chronic diseases is changes in our diet and lifestyle due to industrialization, i.e. pollution of water, food and air.

Over the past few decades, many studies have investigated the possible protective role of spices against chronic diseases. Spices are consumed from seeds, fruits, roots or barks and generally used as food additives for color or as food preservatives. In many regions of the world, spices are used in food products and as medications. They can stimulate the secretion of saliva, promote the digestion, prevent from cold and influenza, and reduce nausea and vomiting. It is well known that spices contain compounds which can fight against oxidation and inflammation which are two main processes for most of chronic diseases. Therefore, they have been described as potent weapons to

fight inflammatory related diseases [1]. Biological effects of spices and their components lay in their ability to induce changes in cellular processes, such as cell division, apoptosis or differentiation. Moreover, their antioxidant capacities are significantly responsible for decreasing the oxidative damage caused by environmental stress.

In this article, health benefits of spices and their constituents will be presented. Use of spices and spice-derived natural compounds in the prevention and treatment of chronic diseases will be discussed as well as their role as possible disease antagonists, when they are introduced with the diet.

2. Spices in traditional medicine

Since the dawn of civilizations spices are used for healing diseases. The earliest evidence of using spices to cure diseases, either through ingestion or inhalation, dates back to Sumerians as early as 5000 BC. Ancient Egyptian (2600 to 2100 BC) widely used garlic and onion to preserve health [2]. In ancient Greece, mint was used for treating digestive system and asthma, garlic against uterine cancer, while rosemary was used for strengthening memory [3]. The Romans cultivated many spices: anise, basil, fennel, bay, garlic, parsley, cumin, dill etc. intended to preserve food and improve health [2].

In Mediterranean region, many spices are traditionally used for treating various diseases: *Satureja montana* (winter savory) against cardiovascular disorders, especially arrhythmia, *Salvia officinalis* for healing heart diseases, nervous system illnesses, kidney and liver problems; *Thymus serpyllum* for strengthening of heart muscle, while *Sanguisorba minor* is used for treating bites of the poisonous local snakes [4]. Oregano, marjoram, summer savory and thyme possess anti-hyperlipidemic properties while hyssop possesses anti-inflammatory and anti-diabetic potential. Basil exhibits anti-aging, anticancer, antiviral, and antimicrobial properties [5].

During the 1st millennium BC, India was a centre of breeding and exporting spices [2], and it remained up to today. Indian traditional medicine (Ayurveda) is based on the use of herbs and spices for health prevention. *Curcuma longa* (turmeric) is widely used for healing rheumatic disorders,

gastrointestinal problems, rhinitis, jaundice etc. [6]. Fenugreek seeds is used in Indian traditionally medicine to reduce blood glucose and lipids as well as to cure diabetes. Garlic, onion, and ginger are known as anticancer agents. Cardamom, black pepper, cumin and mustard were included in Ayurvedic medicine to cure urinary system and jaundice [2], while basil is used to protect heart, cinnamon for circulation, ginger as the universal medicine, particularly relieving nausea and indigestion.

In Chinese ethnomedicine, spices are widely used for centuries. For example, ginseng and *Ginkgo biloba* are used to improve cognitive processes, galangal for abdominal pain, nutmeg for diarrhoea, and cinnamon for colds and flu [3]. Star anise has a long history as a medicinal spice. It is prescribed as a digestive aid and used to promote appetite, to treat abdominal pain, digestive disturbances including colic and to relieve flatulence, for the treatment of emesis and pain, and relieving rheumatic pains [7]. Fennel, with carminative properties, is used for treating gastrointestinal disorders, as diuretic and potential drug for hypertension [8]. Cinnamon bark may be used alone or with other herbs for relieving digestive tract problems due to microbial infections, treating diarrhea or improving blood circulation [9] **(Table 1).**

Number of spices are used in ethnomedicine in Africa. Such as, in Ethyopia, basil, is often used against headache and malaria, black mustard (*Brasica nigra*) against stomach ache, constipation, bloating, amoebic dysentery and abortifacient, *Cinnamomum zelanicum* for treating cold symptoms, *Trigonella foenum-graceum* against stomachache, antispasmodic, powder used for wound dressing, *Allium sativum* against malaria, cough, hypertension, wounds, asthma, parasitic infections, toothache, diabetes, hemorrhoids while *Mentha piperita* is used against cold and headache [10].

Native Americans used spices for thousands of years. They used sage to heal problems of the stomach, colon, kidneys, liver, lungs, skin and believed that sage may protect them against bad spirits. Lemongrass with strong anti-fungal properties are used for healing fungal infections, but also as a pesticide and preservative. Ginger, fenugreek, wild garlic and onion, mint and many other spices are used as medicinal remedies [11].

In Latin America many spices are traditionally used, such as huacatay (*Tagetes minuta*) which possess very strong anti-hyperglyc effect, ginger (*Zingiber officinale*) significantly inhibited the hypertension, pepper (*Capsicum*) and (*Piper angustifolium*) exhibit anti-hyperglycemia and anti-hypertension potential [12].

3. Therapeutic roles of spices: diseases prevention and treatment

In the last decades, the fast development of molecular and analytical techniques allowed modern medicine to understand and explain better why spices have been so important in the traditional medicine. In fact, besides antimicrobial activity of spices, anti-inflammatory, antiviral, anti-diabetic and anti-carcinogenic have also been proposed [14] (**Table 1**).

The first aspect concerning the beneficial effects of spice-derived compounds is their bioavailability. For this reason, spice constituents need to be released by the food matrix before performing their activity. Gawlik-Dziki (2014) [15], studied the bioaccessibility and bioavailability of phenolic compounds from marjoram, thyme, ginger, and black pepper in *in vitro* model simulating gastrointestinal conditions and intestinal absorption. The gastro-intestinal digestion caused a progressive release of natural compounds. In particular, the total phenols, flavonoids and phenolic acids contents were higher in ginger and marjoram extracts, followed by pepper. The intestinal absorption did not affect dramatically the contents of natural compounds, which in turn were also able to activate superoxide dismutase and catalase (involved in the enzymatic defence system) and to inhibit lipoxygenase and xanthine oxidase (pro-oxidant enzymes). The activation of antioxidant enzymes together with their intrinsic antioxidant properties represents one of the mechanisms of action that spices posses against human diseases, such as inflammation. Inflammation is a physiologic process that, once it become chronic, can lead to cancer, arthritis, aging, cardiovascular, neurological and metabolic diseases [15].

Arranz et al. (2014) [16] reported the anti-inflammatory properties of supercritical CO_2 extracts obtained from sage (*Salvia officinalis*) *in vitro*. In other studies, curcumin attenuated

inflammation in lipopolysaccharide-induced mastitis in mice [17], and ginger improved TNBS-induced colitis [18]. Mueleret al., (2010) [19], reported that chili pepper extract had high anti-inflammatory potential, followed by allspice, basil, bay leaves, black pepper, licorice, nutmeg, oregano, sage and thyme. If the antioxidant property of spices is responsible for most of their healthy effects, recent literature suggests that they may act also as cell modulators, or cell signals [1] (**Fig. 1**). The targets related to inflammation are mainly tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-10 and cyclooxygenase-2 (COX-2). For example, Mueller, et al., (2010), [19], reported that chili pepper extract (0.2 and 0.5 mg/mL) had high anti-inflammatory potential reducing IL-6 and TNF-α, COX-2, while enhancing IL-10. Also, allspice, basil, bay leaves, black pepper, licorice, nutmeg, oregano, sage and thyme extracts were able to modulate the secretion of cytokine. The compounds apigenin, capsaicin, diosmetin, luteolin, and quercetin moderately reduced IL-6 and TNF-α while rosmarinic acid increased secretion of IL-10 [20]. Other than those related to inflammation and oxidation, various molecules with different functions and belonging to different pathways have been described (**Fig. 1**). Therefore, it is not surprising that spice-derived natural compounds modulating such targets can also play a key role in preventiuon and treatment of different diseases [14, 21] (**Fig. 2**).

3.1. Role of spices against cancer

The use of spices remedies is becoming more and more common among patients with cancer [21]. According to Mueller, Hobiger & Jungbauer (2010), [19] a diet rich in spices may contribute to the reduction of the inflammatory response and its related diseases. This would explain why the risk of cancer is higher in western than in eastern countries [21]. Anticancerogenic effects of many spices and spice derived natural compounds have been proved *in vitro* and in animal models. Although convincing human trials are still missing, studies of natural compounds, or their synthetic analogues, and combinations with other drugs are constantly under development [22]. Spices constituents, such as curcumin, have demonstrated their potential against several types of cancers including leukemia,

lymphoma, melanoma and sarcoma (**Fig. 2**). They can act at different stages of cancer development (initiation, survival, proliferation, metastasis and angiogenesis) by affecting the crosstalk of several pathways.

NF-κB is one of the most important links between inflammation and cancer. It plays a role in cancer initiation and progression since it regulates the expression of genes involved in the transformation, survival, proliferation, invasion, angiogenesis and metastasis of tumour cells. Compounds such as curcumin, capsaicin, zerumbone, eugenol, isoeugenol, cardamonin, ursolic acid and caffeic acid, inhibit NF-κB signalling pathway. Therefore, they were tested and subsequently proposed as a therapeutic strategy for preventing tumour development [17, 18]. Curcumin, for instance, can also regulate the cell survival through pro- and anti-apoptotic factors (i.e. Bcl-2, Bcl-xL, Bax, caspases 8, 3, 9), tumour suppressors (i.e. p53 and p21) and death receptors (i.e. DR4 and DR5) [21]. Several targets associated with cell proliferation, metastasis and angiogenesis have also been described.

Signal Transducer and Activator of Transcription 3 (STAT3), a transcription factor associated with invasion, angiogenesis, metastasis, cellular transformation, survival and proliferation is suppressed, directly or indirectly, by capsaicin, diosgenin, thymoquinone, curcumin and ursolic acid [20]. AP1, associated with tumour proliferation and angiogenesis, is inhibited by curcumin and ursolic acid. Vascular endothelial growth factor receptor (VEGFR) and insulin-like growth factor-1 receptor (IGF-1R) play a role in vasculogenesis, angiogenesis and metabolism of glucose, fat, and protein. The activity of these receptors is regulated in several ways: directly, inhibiting their activation (cinnamon extract/VEGFR2, ursolic acid/EGFR), or indirectly, decreasing the secretion of the ligands (curcumin/IGF-1R and kaempferol/VEGFR) [20, 21].

Finally, targets related to the energy and metabolisms of the cells were reported. For example, AMP-activated protein kinase (AMPK), the sensor of cellular energy status, is reported to be activated by curcumin [20]. Moreover, Vishvakarma et al. (2014), [23] described that curcumin can play an

antitumor role altering glucose uptake and its metabolism in tumour cells. This perturbation leads to an altered pH homeostasis and reversal of lactic acidosis that, at last, induce apoptosis.

3.2. Role of spices against arthritis

Arthritis generally means inflammation of the joints and it can describe over a hundred different diseases. It affects bones, entheses and tendons. Promising results using spices to treat arthritis has been described (**Table 1** and **Fig. 2**). Curcumin possesses antirheumatic and antiarthritic effects. It acts mainly on targets such as NF-κB, TNF-α, AP-1, Egr-1, chemokines, 5-LOX, iNOS, and COX2. *In vitro* studies showed that it downregulates Bcl-2 and XIAP (anti-apoptotic molecules) while it up-regulated Bax (pro-apoptotic). On the contrary, according to *in vivo* studies, curcumin supressed IFNγ-induced BAFF expression together with the phosphorylation and translocation of STAT1 [22]. Crude ginger extract and gingerol reduced joint swelling in an animal model of rheumatoid arthritis, while capsaicin gel was reported to be effective on patients with mild to moderate knee osteoarthritis [24]. Combination of anti-inflammatory drugs and natural compounds had also shown promising results. Curcumin and carvacrol, for example, may enhance the antiarthritic action of methotrexate. In particular, carvacrol (active compound of oregano) reduces the toxic side effects of methotrexate and promotes its safety [22, 25]. It can be concluded that the large number of natural products may be used a golden source for the treatment of arthritis.

3.3. Role of spices against cardiovascular diseases

The role of spices in cardiovascular diseases (i.e. atherosclerosis, myocardial infarction, cariomyopathy and stroke) has also been investigated (**Table 1 and Fig. 2**). For instance, carvacrol was able to protect from myocardial infarction and to decrease the heart rate and blood pressure in animal models. Moreover, it can promote the activation of TRPV cation channels and the suppression of calcium ion currents in the endothelium, in turn inducing relaxation of the arteries. All these functions seem to depend on its antioxdative and antiapoptotic properties [25]. Also, capsaicin,

through the activation of TRPV1 channels, is involved in the phosphorylation of endothelial nitric oxide synthase (eNOS) in rats, a key element for maintaining cerebral blood flow and preventing stroke [26].Curcumin,studied *in vitro* as well as preclinical and clinical tests,has shown effecs against myocardial infarction and atherosclerosis, through the inhibition of peripheral blood mononuclear cells and vascular smooth muscle cells proliferation. Moreover, its consumption was associated with a significant reduction in circulating C-reactive protein levels and activation of SIRT1, markers of possible cardiovascular diseases [22]. All these results suggested both curcumin and carvacrol as promising cardioprotective agents.

3.4. Role of spices against neurodegenertive diseases

Neurodegenerative diseases are progressive disorders of the central nervous system with cognitive, motor and behavioral dysfunctions. These diseases include Alzheimer's (AD) and Parkinson disease (PD) and less common amyotrophic lateral sclerosis and Huntington's disease.

Several *in vivo* and *in vitro* studies showed the potential of spices for neurodegenertive diseases (**Table 1 and Fig. 2**).

3.4.1. Role of spices against Alzheimer disease

Alzheimer disease is a degenerative disease of the brain that causes dementia. Memory loss is the most common sign of Alzheimer disease which have more then 27 million people all around the world, mainly older than 65 years. It comprises with numerous amyloid plaques (amyloid β) in the cerebral cortex, neurofibrillary tangles and neuronal loss [27].

Curcumin can act on various target sites that lead to amelioration of Alzheimer disease, suppressing oxidative damage, inflammation, cognitive deficits and amyloid accumulation [22]. The neuroprotective effects of curcumin on *β*-amyloid toxicity may involve *β*-catenin and PI3K/Akt signalling pathways. In particular, it was detected an increased free form of *β*-catenin, that promotes

cell survival, and an enhanced activation of Akt, that in turn prevents the degradation of β-catenin [28].

Beneficial effect of saffron on the Alzheimer patient's during one year was significant. Efficasy of saffron was similar like memantine (drug used for treating dementia of AD) in patients with moderate to severe AD [29]. There is a number of studies of antidepressant potential of saffron. [30, 31, 32] Depression is very frequent symptoms in AD patients (more than 50 % of patient are diagnosed with depression). About usefull effects of saffron in AD reported Akhondzadeh et al., (2010) [33]. Saffron produced significant effects on cognitive functions (after 16 weeks of treatment) in comparison to placebo-control. Coriander seed extract show protection of pyramidal cells in cerebral cortex against Alzheimer's induced by AlCl treatment [34].

On the other hand, carvacrol inhibited acetylcholinesterase, a key compound involved in neurotransmission; modified the permeability of calcium ion channels involved in neuronal cell death in mice, enhancing in this way the recovery of traumatic brain injury; interacted with dopaminergic brain pathways, inducing antidepressant effects [25]. [6]-gingerol and thymoquinone protect cells against cytotoxicity and apoptosis. Capsaicin protects against neurological impairment and reduces stress-induced cognitive and Alzheimer disease-like pathological alterations. Piperine was shown to protect against epilepsy-associated depression; this antidepressant activity was likely due to piperine's activity as a monoamine oxidase inhibitor and its neuroprotective properties [24].

3.4.2. Role of spices against Parkinson's disease

Parkinson's disease is a chronic, degenerative, neurological disorder which is characterized by the cumulative loss of dopaminergic neurons. Genetic as well as environmental factors (neurotoxic pollutants) may be the reasons of PD. Different natural compounds from the spices possess neuroprotective potential (flavonoids, alkaloids, caffeine, xanthones, saponins, isoflavonoids, catechins, anthocyanins, curcuminoids, zingerone and many others) [35].

The main components in black caraway (*Nigella sativa*), thymoquinone, showed preventive effect against dopaminergic neuronals against MPP^+ (1-methyl-4-phenylpyridinium) in PD rat models [35]. Sesamin, bioactive component from *Sesamum indicum* with immunomodulatory effects, precludes NO synthase (iNOS) protein expression in neuronal cells and reduces mRNA levels of the potent pro-inflammatory cytokine interleukin-6 (IL-6) in microglial cells [35]. *Zingiber officinale* (ginger) exhibits strong neuroprotective effect. Compounds zingerone and 6 shogaol which are isolated from ginger prevent apoptopic neural cell death (throught doppamine loss) in mouse striatum. These compounds also avert 6-OHD induced doppamine loss in mouse striatum and prevent apoptotic neural cell death. Zingerone shows lipid peroxidation lowering effect which is in connection to its cytoprotective effect [35].

Curcuminoids isolated from *Curcuma longa* possess different cytoprotective activities. Neuroprotective mechanisms of curcumin in PD are various. Curcumin demonstrates a disease-modifying effect throught dopaminergic neurons against LPS and α-synuclein induced neurotoxicity, soothing dopamine loss, which facilitate oxidative stress and limits mitochondrial dysfunction in *in vitro* and *in vivo* models of PD [35] Some studies confirm that neuroprotective effect of curcumin against PD is in connection with its antioxidant activity. *In vivo* experiments on MES (mouse embryonic stem) cells treated with curcumin highly increase expression of Cu-Zn superoxide dismutase and decrease intracellular ROS (Reactive oxygen species) accumulation [36] In Parkinson's disease is present accumulation of oxidative DNA damage, while Cu and Fe ions preclude the DNA repair enzymes. It has been proved that curcumin can change inhibition of DNA repair enzymes in neuroblastoma cells [36].

3.4.3. Role of spices against Amyotrophic lateral sclerosis (ALS)

Motor neurons in motor cortex of brain, brain stem and spinal cord are stricken in Amyotrophic Lateral Sclerosis (ALS) [37].

Bhatia et al., (2015) [37] reported that curcumin inhibits the growth of amyloid fibrils of superoxide dismutase (SOD1) which leads in formation of unstructured aggregates of SOD1. Rayleigh Light Scattering and Dynamic Light Scattering studies showed formation of pre-fibrillar aggregates in samples whith curcumin. Curcumin possess ability to strongly connect with the oligomers and pre-fibrillar aggregates (which is evident from curcumin fluorescence data). The authors assumed that molecules of curcumin interact with amyloidogenic stretches in the unaggregated SOD1 and thus interfere with early nucleation. Curcumin strongly connect to this aggregation and block the place which is exposed to aggregation.

Many literature data show curcumin's protective effect as free radical scavenger and its cytoprotective potential Often genetic mutation in ALS are located in Cu, Zn superoxide dismutase (SOD1) gene. SOD1 convert $O_2^{\bullet -}$ to H_2O_2 and decomposed to water. Curcumin reduce the ROS production, stimulate antioxidant processess and protect against oxidative damage. Curcumin may increase mitochondrial activity and Nrf2 expression which leads to increased expression of cytoprotective proteins and thus limit the risky effects of free radicals [38].

3.4.3. Role of spices against Huntington's disease

Huntington's disease (HD) is a progressive, neurodegenerative hereditary disorder that affects the coordination of muscles and leads to the mental disfunctions with characteristic behavior symptoms. Disfunction in mitochondria is one of the main reasons of HD diseases.

Sandhir et al., (2013) [39] investigated impact of CSLNs (curcumin encapsulated solid lipid nanoparticles) on improving 3-nitropropionic acid (3-NP)-induced HD *in vivo* in rats models. 3-NP is a well known fungic toxin causing neurotoxicity. Animals treated with C-SLN showed high level of increasing mitochondrial activity. Reduction in mitochondrial swelling, lipid peroxidation and reactive oxygen species (ROS) is also observed in animal models treated with C-SLNs. Synergistically effect of curcumin and piperine (which enhance bioavailability), moderate 3-

nitropropionic acid-induced neurotoxicity in rats [40]. Curcumin with immense neuroprotective potential, in a Drosophila model of HD, improves disease symptoms with suppress cell death which leads to stopping of the progression of Huntington's disease [41].

Curcumin, as powerful antioxidant may be used as a potential supplement to treat HD, and other neurodegenerative disorders.

3.5.Role of spices against metabolic diseases

Disorders of energy utilization and storage, such as obesity, diabetes, hyperlipidemia, hypoglycemia, increase the risk of developing cardiovascular disease. Comparing to other diseases, few spices possess significant hypocholesterolemic and hypotriglyceridemic properties (**Table 1**). For example, a reduction or increased resistance in LDL oxidation was observed in studies *in vitro* and in humans, respectively, using garlic and garlic compounds [42]. S-methyl cysteine sulfoxide, obtained by onion, caused increased catabolism of lipids reduction of endogenous lipogenesis, whereas capsaicinoids, from red pepper, decreases cholesterol absorption [42]. A significant hepatoprotective and hypolipidemic effect was reported for carvacrol. In particular, feeding hepatotoxic rats with carvacrol for 21 days increased the levels of VLDL and LDL and decreased HDL in serum. Moreover, no changes in metabolic enzymes associated with obesity and diabetes were reported when carvacrol and an antidiabetic drug (rosiglitazone) were administered to rats following a high-fat diet. The combined effect had a higher antihyperglycemic potential than the individual compounds. Finally, carvacrol has been proposed as a possible help against obesity since reduced body weight gain and plasma lipid levels in mice fed with a 0.1% carvacrol- supplemented diet [25].

3.6.Role of spices in aging

The aging process is universal for almost all multicellular organisms, in which the biological function of all organs undergoes gradual impairment mitigating the ability to maintain homeostasis and resulting in an increased risk of death. One of the earliest and most plausible explanations for the mechanistic basis of aging is the ‘‘free radical theory of aging’’. This theory predicts that ROS generated by mitochondria lead to mitochondria dysfunction, which elicits aging and the onset of age-related diseases [43]. Moreover aging is associated with changes in lipid peroxidation, lipofuscin, NO, GSH level as well as enzyme activities such as SOD, GPx, GST, CAT and Na^+, K^+, ATPase activities [44]. The level of inflammatory cytokines, such as IL-1 and TNF-α, also increases with aging, thus indicating an association between inflammation and aging [21]. However, not too many studies have been published regarding this aspect. Among those present in literature, curcumin and its primary metabolite tetrahydrocurcumin (THC) showed the capability to increase mean lifespan in three model organisms: the mouse, the nematode roundworm and Drosophila. Life-span extension was associated with the up-regulation of stress response genes and the down- regulation of age-related genes [43]. Bala (2014), [44] instead, studied the effect of garlic and turmeric, and their main constituents, on rat brain aging. Present finding supports the concept that different brain regions exhibit different regional vulnerability to peroxidative reactions as a function of age. Garlic and turmeric with their functional component diallylsulphide and curcumin, respectively, inhibit lipid peroxidation, 4-HNE and NO level in aging brain, while they enhances GSH level and antioxidative enzymes (i.e. GST, SOD) activities. All the treatments have shown reduced accumulation of intraneuronal lipofuscin pigment and reversal of age-related changes known to occur at cellular level [44].

3.7. Spices and possible side effects

Spices and their bioactive components have a very broad spectrum of activities. However, some researches reported the possible toxicity of few them, mainly in the form of essential oils and/or

pure compounds [45]. For instance, thymol or eugenol may cause mouth tissues irritation when are used in root canal treatment. Moreover, carvacrol, cinnamaldehyde, carvone and thymol exhibited moderate toxic effects at the cellular level *in vitro* but not *in vivo* [45]. The use of ginger tea in rats, from day 6 of gestation up to day 20, did not show maternal toxicity but increased the early embryo loss [46, 47]. Orally dose of 400 mg of ginger 3 times per day for two weeks have been used as clinical trial on humans and possible mild diarrhea, heartburn and gastric irritantion were described [48].

Regarding curcumin, some data showed that overdoses cause nausea, diarrhea, liver dysfunction, hypotension, increased menstrual flow etc. Martins (2018), [49] noticed that toxic curcumin effects may be in connection with ingestion of other spices. From a neurodegenerative point of view curcumin therapy is acceptable because of its nontoxic effect at high concentrations and may easy crosses the blood–brain barrier [50, 51, 52].

4. Conclusion

Spices are not only food aditives that improve taste and smell of food. They represent historical seals of different cultures that have an important impact on human health. The use of spices or active compounds as modulators of physiological responses and biological pathways has been studied extensively *in vitro* and in animal trials. To exert their functionality in the body, these compounds must be bioaccessibile (successfully released from the food matrix/delivery system) and bioavailabile (being absorbed in the gastrointestinal tract, GIT). The latter aspect is crucial for the final bioactivity. Therefore, together with *in vitro* test focusing on the final effect of spices, it would be essential to study their stability and activity during the passage throughout the GIT [53].

In the last years, researchers focused their studies on GIT and in particular on the colon region. Here, the gut microbiome represents a fundamental part of our body that is able to impact human health. For instance, polyphenols are only partially absorbed in the small intestine (5-10%) and then transferred into the colon. Here, bacteria transform the original molecules so that the resulting

polyphenols, rather than the original compounds found in foods, provide beneficial effects on health [54]. Therefore, it should not surprise that the gut microbiome has been described as a novel human organ [55]. In fact, dysbiosis of the microbiome have been associated with several metabolic, chronic and degenerative diseases [56]. All these diseases are related with inflammation processes. Spices and their derivatives can induce changes in cellular processes, and posses significant antioxidant capacities. Some clinical studies have already proposed spice constituents, such as curcumin, as promising therapeutic agents [22]. However, further work targeted to identify efficacy, dose and safety of these compounds cannot forget the impact that spices may exert on the human microbiome and the way back around.

Finally, the combination of different natural compounds with novel technologies, synthetic compounds [57] and natural derivatives [58] have already been described for food preservation [59]. The same approach can be useful to enhance the target specificity and efficacy of spices and spices derivatives in chronic diseases.

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Figure Legends

Fig. 1. Molecular targets of spices and their constituents.

Fig. 2. Health beneficial effects of spices and their active components against various chronic diseases.

Figure 1

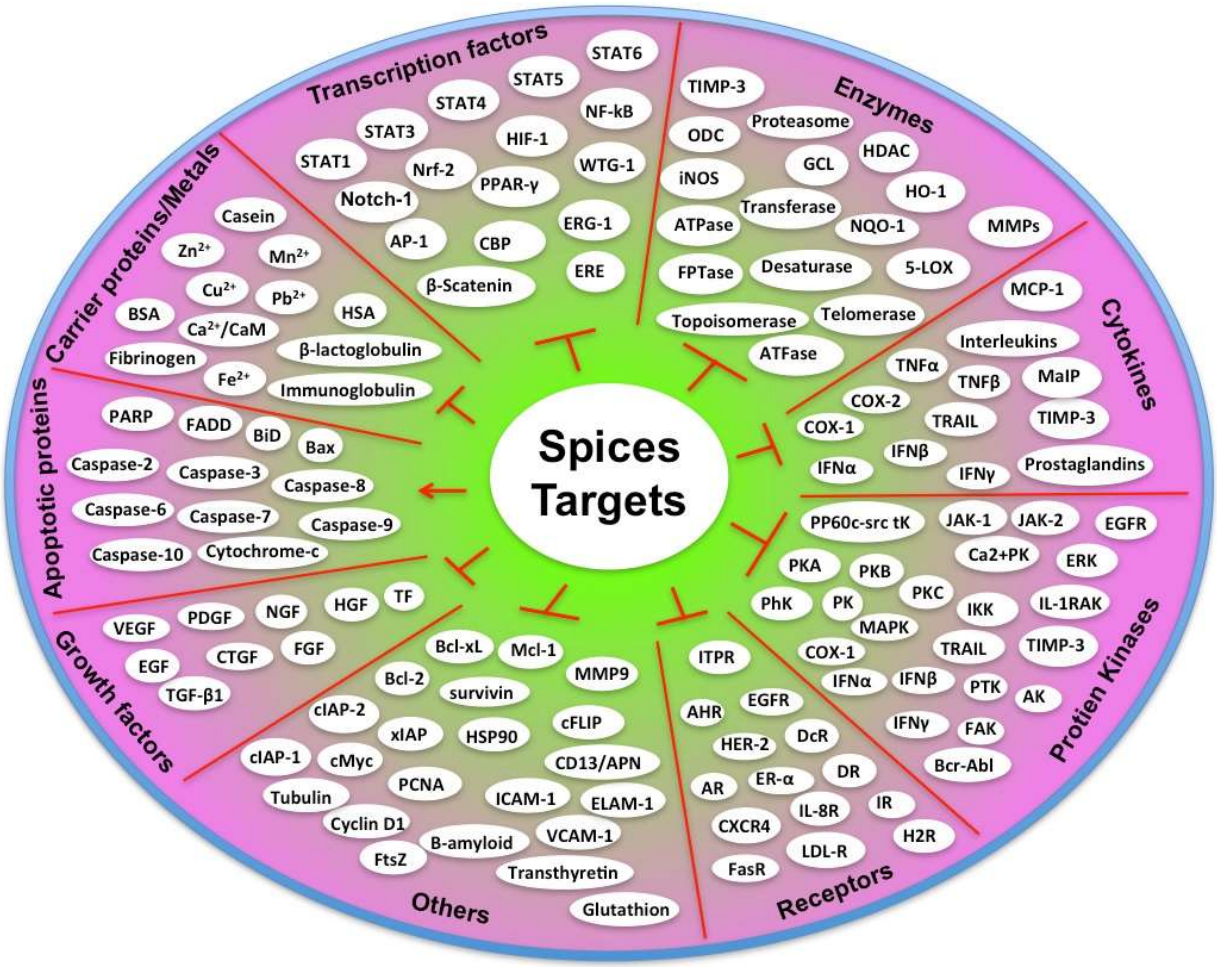
Spices
Targets
Transcription factors
STAT6
STAT5
STAT4
NF-kB
STAT3
HIF-1
STAT1
Nrf-2
WTG-1
PPAR-γ
Notch-1
ERG-1
AP-1
CBP
ERE
β-Scatenin
Enzymes
TIMP-3
Proteasome
ODC
HDAC
GCL
iNOS
HO-1
Transferase
ATPase
NQO-1
MMPs
FPTase
Desaturase
5-LOX
Topoisomerase
Telomerase
ATFase
Cytokines
MCP-1
Interleukins
TNFα
TNFβ
MaIP
COX-2
TRAIL
TIMP-3
COX-1
IFNβ
IFNα
IFNγ
Prostaglandins
Protien Kinases
PP60c-src tK
JAK-1
JAK-2
EGFR
Ca2+PK
ERK
PKA
PKB
PKC
PhK
PK
IKK
IL-1RAK
MAPK
TRAIL
TIMP-3
COX-1
ITPR
IFNα
IFNβ
PTK
AK
EGFR
AHR
IFNγ
FAK
HER-2
DcR
Bcr-Abl
ER-α
DR
AR
IL-8R
IR
CXCR4
H2R
LDL-R
FasR
Receptors
Others
Glutathion
Transthyretin
B-amyloid
VCAM-1
FtsZ
Cyclin D1
ICAM-1
ELAM-1
Tubulin
PCNA
CD13/APN
cIAP-1
cMyc
cFLIP
cIAP-2
xIAP
HSP90
Bcl-2
survivin
MMP9
Bcl-xL
Mcl-1
Growth factors
VEGF
PDGF
NGF
HGF
TF
EGF
CTGF
FGF
TGF-β1
Apoptotic proteins
PARP
FADD
BiD
Bax
Caspase-2
Caspase-3
Caspase-8
Caspase-6
Caspase-7
Caspase-9
Caspase-10
Cytochrome-c
Carrier proteins/Metals
Casein
Zn2+
Mn2+
Cu2+
Pb2+
BSA
Ca2+/CaM
HSA
Fibrinogen
β-lactoglobulin
Fe2+
Immunoglobulin

Figure 2

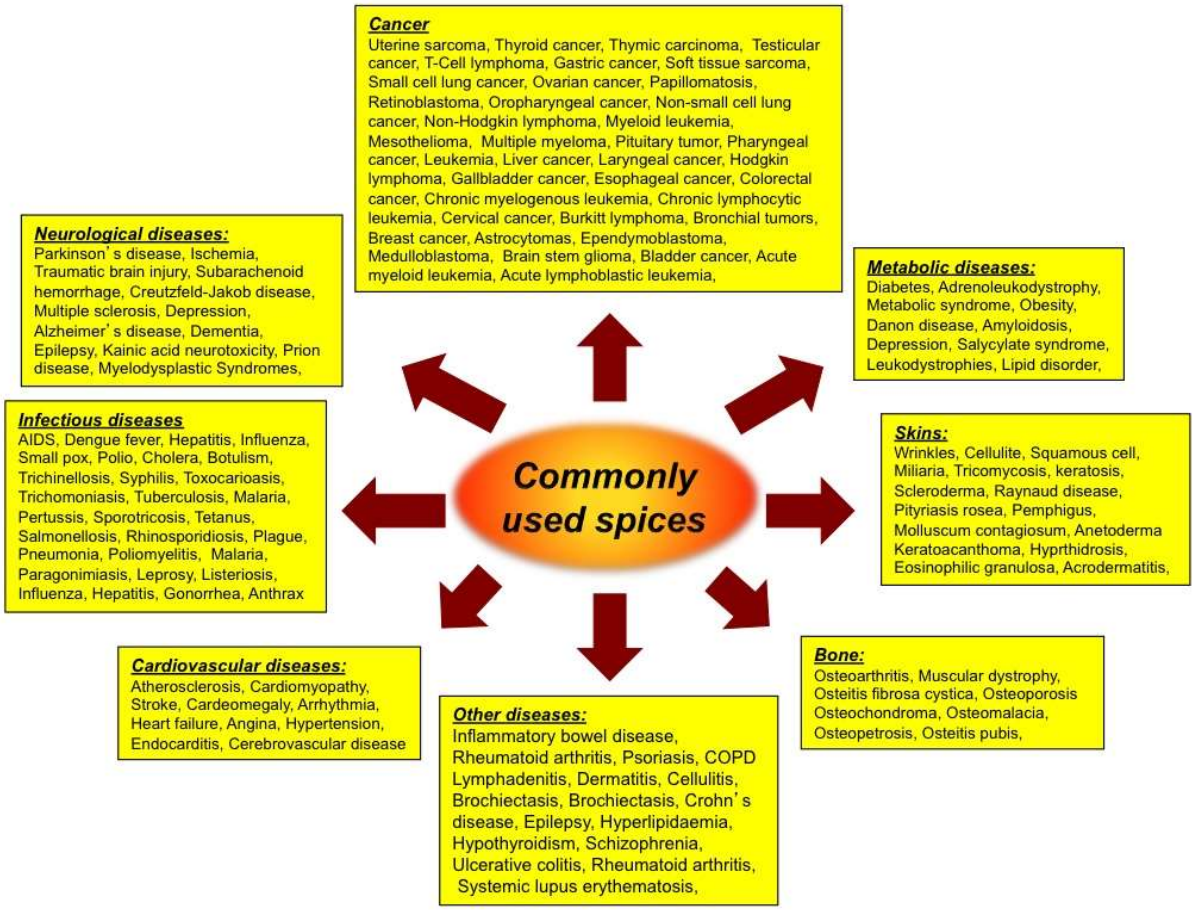
Cancer
Uterine sarcoma, Thyroid cancer, Thymic carcinoma, Testicular cancer, T-Cell lymphoma, Gastric cancer, Soft tissue sarcoma, Small cell lung cancer, Ovarian cancer, Papillomatosis, Retinoblastoma, Oropharyngeal cancer, Non-small cell lung cancer, Non-Hodgkin lymphoma, Myeloid leukemia, Mesothelioma, Multiple myeloma, Pituitary tumor, Pharyngeal cancer, Leukemia, Liver cancer, Laryngeal cancer, Hodgkin lymphoma, Gallbladder cancer, Esophageal cancer, Colorectal cancer, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Cervical cancer, Burkitt lymphoma, Bronchial tumors, Breast cancer, Astrocytomas, Ependymoblastoma, Medulloblastoma, Brain stem glioma, Bladder cancer, Acute myeloid leukemia, Acute lymphoblastic leukemia,
Neurological diseases:
Parkinson's disease, Ischemia, Traumatic brain injury, Subarachenoid hemorrhage, Creutzfeld-Jakob disease, Multiple sclerosis, Depression, Alzheimer's disease, Dementia, Epilepsy, Kainic acid neurotoxicity, Prion disease, Myelodysplastic Syndromes,
Metabolic diseases:
Diabetes, Adrenoleukodystrophy, Metabolic syndrome, Obesity, Danon disease, Amyloidosis, Depression, Salycylate syndrome, Leukodystrophies, Lipid disorder,
Infectious diseases
AIDS, Dengue fever, Hepatitis, Influenza, Small pox, Polio, Cholera, Botulism, Trichinellosis, Syphilis, Toxocarioasis, Trichomoniasis, Tuberculosis, Malaria, Pertussis, Sporotricosis, Tetanus, Salmonellosis, Rhinosporidiosis, Plague, Pneumonia, Poliomyelitis, Malaria, Paragonimiasis, Leprosy, Listeriosis, Influenza, Hepatitis, Gonorrhea, Anthrax
Commonly used spices
Skins:
Wrinkles, Cellulite, Squamous cell, Miliaria, Tricomycosis, keratosis, Scleroderma, Raynaud disease, Pityriasis rosea, Pemphigus, Molluscum contagiosum, Anetoderma Keratoacanthoma, Hyprthidrosis, Eosinophilic granulosa, Acrodermatitis,
Cardiovascular diseases:
Atherosclerosis, Cardiomyopathy, Stroke, Cardeomegaly, Arrhythmia, Heart failure, Angina, Hypertension, Endocarditis, Cerebrovascular disease
Bone:
Osteoarthritis, Muscular dystrophy, Osteitis fibrosa cystica, Osteoporosis Osteochondroma, Osteomalacia, Osteopetrosis, Osteitis pubis,
Other diseases:
Inflammatory bowel disease, Rheumatoid arthritis, Psoriasis, COPD Lymphadenitis, Dermatitis, Cellulitis, Brochiectasis, Brochiectasis, Crohn's disease, Epilepsy, Hyperlipidaemia, Hypothyroidism, Schizophrenia, Ulcerative colitis, Rheumatoid arthritis, Systemic lupus erythematosis,

Table 1. Traditional use/health benefits of spices

Name of spices (Scientific and common)	Use of spies in traditional medicine/ chronic disease prevention	Reference(s)
1. *Allium sativum* (Garlic)	Intestinal worms, colic, flatulence, dysentery, liver disorders, tuberculosis facial paralysis/antiarthitic antithrombotic, hypolipidemic, anticancer, anti-aging antiarthritic, hypoglycemic	[42, 44, 60]
2. *Allium schoenoprasum* (Chives)	Mild antiseptic, antiproliferative anti-inflammatory, anticancer, anthelmintic and antihypertensive	[61, 62]
3. *Alpinia galanga* (Greater galanga)	Rheumatism, bronchial catarrh useful in case of dyspepsia, preventing vomiting/ anti-inflammatory, anticancer	[63]
4. *Amomum subulatum* (Black cardamom)	Cardiac stimulant, carminative, stomachic, diuretic, anticancer, analgesic, anti-inflammatory, antiulcer, antimicrobial, antidiabetic, hypolipidaemic	[64, 65]
5. *Angelica archangelica* (Angelica)	Carminative, diaphoretic, emmenagogue, stomachic and tonic/ antitumor, cytotoxic, hepatoprotective, antiulcer, antimutagenic	[66]
6. *Anethum graveolens* (Dill)	Carminative, stomachic and diuretic anti-inflammatory	[67, 68, 69]
7. *Apium graveolens* (Celery seed)	Diuretic, stimulant, sedative/ hepatoprotective, anticancer, cytotoxic, antiseptic carminative, emmenagogue, sedative	[70]
8. *Armoracia rusticana* (Horseradish)	Urinary infections, diuretic, for coughs and bronchitis gout and rheumatism, sinus congestion, anti-influenza for treating flu and liver disease	[71]
9. *Artemisia dracunculus* (Tarragon)	Digestive stimulant, insomnia, skin wounds, irritations, allergic rashes, antiepileptic, antispasmodic/anti-inflammatory, hepatoprotective, antihyperglycemic	[72]
10. *Boesenbergia rotunda* (Fingerroot)	Rheumatism, muscle pain, febrifuge, gout, gastrointestinal disorders, flatulence, carminative, stomach ache, dyspepsia, peptic ulcer/ antiparasitic, antiulcer, anticancer	[73]
11. *Brassica juncea* (Brown mustard)	Abdominal pain, anorexia,diseases of the spleen, /anticancer	[74, 75]
12. *Brassica nigra* (Black mustard)	Rheumatism, sciatica, peritonitis, neuralgia rheumatism and migraine	[76]
13. *Bunium persicum* (Black cumin)	Colic pain and dysmenorrheal/ anti-inflammatory	[77]
14. *Capsicum annuum* (Chilli pepper)	Bronchitis, arthritis, diabetes, fatigue, and sore throats/ anticancer, anti-inflammatory protect from cardiovascular diseases , anticancer	[19, 78, 79]
15. *Carum carvi* (Caraway)	Gastrointestinal problems, indigestion, carminative diuretic, anti-spasmodic, galactogogue	[80]
16. *Cinnamomum aromaticum* (Cassia)	Diarrhea, digestive problem/ anti-inflammatory, hepatoprotective, antiulcer, anticancer anti-HIV, anti-diabetic, antiallergic, immunomodulatory	[81]
17. *Cinnamomum burmannii* (Indonesian cinnamon)	Nausea, flatulent dyspepsia, coughs, chest complaints, diarrhea gripe, and malaria/anti-inflammatory, analgesic, and anti-diabetic, antitumor	[82]
18. *Cinnamomum verum* (Cinnamon)	Astringent, carminative,against colds, diarrhea	[83, 84]
19. *Citrus hystrix* (Kaffir lime)	improve digestion/ cholinesterase inhibitory anticancer, chemopreventive, cardio, hepatoprotective	[85, 86]

20. *Ceratonia siliqua* (Carob tree)	Digestion problems, heartburn, and the intestine's inability to properly absorb certain nutrients from food /cytotoxic	[87]
21. *Citrus aurantifolia* (Lime)	Obesity, arthritis, gout, rheumatism, anxiety and insomnia, hypertension, anticancer	[88]
22. *Coriandrum sativum* (Coriander)	Physiological disorders, diabetes, increased cholesterol, arteries blockage, urinary tract problems, skin problems swelling prevention, anti-osteoporosis, liver diseases anticancer, hepatoprotective	[89, 90, 91]
23. *Crocus sativus* (Saffron)	Antispasmodic, expectorant, for treatment of stomach ailments /cytotoxic, anti Alzheimer's, hypolipidemic antinociceptive, anti-inflammatory, cardioprotective anti Parkinson's, anticance	[92, 93]
24. *Curcuma longa* (Turmeric)	Skin, pulmonary, gastrointestinal systems aches, pains, wounds, sprains, liver disorders anti-inflammatory anticancer (colorectal, pancreatic, breast cancer, multiple myeloma) antimutagen, neuroprotective, Alzheimer disease, neuroprotective,	[22, 42, 94, 95, 96]
25. *Cuminum cyminum* (Cumin)	Indigestion, jaundice, diarrhea, /anticancer, antidiabetic, anti-osteoporotic	[97]
26. *Cymbopogon citrates* (Lemon grass)	Skin disorders, regulate digestion fevers and headaches, and relieve coughs anti-mutagenicity, hypoglycemic, anti-inflammatory	[98]
27. *Eruca sativa* (Rocket)	Eye infections, digestive and kidney problems/ anti-ulcer, anticancer	[99, 100]
28. *Eryngium foetidum* (Long coriander)	Stomach pains, hypertension rheumatism, asthma, eye disease, /antiinflammatory activity, analgesic,	[101, 102]
29. *Ferula asafetida* (Asafoetida)	Hysteria and whooping cough and to treat ulcers, antispasmodic, diuretic, antiepileptic, anthelmintic, to treat cough, asthma, and bronchitis /anticancer, hepatoprotective, hemopreventive anti-HIV, antileukemic	[103, 104]
30. *Foeniculum vulgare* (Fennel)	Gastrointestinal disorders antithrombotic, hepatoprotective	[8]
31. *Garcinia indica* (Kokum)	Relieve sunstroke, remedy for dysentery, an appetizer, liver tonic, cardiotonic	[105, 106]
32. *Heracleum persicum* (Golpar)	Relieve pains, and swellings/ anticonvulsant, Immunomodulatory, anti-inflammatory anti-inflammatory,	[107, 108]
33. *Hyssopus officinalis* (Hyssop)	Bronchitis, asthma, digestive ailments, insomnia, diabetes /anticancer	[109, 110]
34. *Houttuynia cordata* (Chameleon plant)	Cholere, dysentery, curing of blood deficiency coughs, dysentery, enteritis and fever/anti-leukemic, anti-cancer	[111, 112]
35. *Illicium verum* (Star anise)	Respiratory tract infections, lung swelling cough, bronchitis, the flu (influenza) /	[7, 113]
36. *Kaempferia galanga* (Kencur)	Sore throat, swellings, rheumatism, eye infections, /anti-inflammatory, anticancer, antihypertensive	[114, 115]
37. *Laurus nobilis* (Bay)	anti-helminthic, anti-tussive, anti-rheumatic, anti-inflammatory, antiulcerogenic, anticonvulsant, antimutagenic	[19, 116]
38. *Lavandula angustifolia* (Lavender)	Sedative, carminative, anti-depressive, anti-inflammatory, analgestic	[117]
39. *Limnophila aromatica* (Finger grass)	Anorexia, dyspepsia, helminthiasis, constipation, inflammations/ vascular protective	[118]
40. *Lippia adoensis* (Koseret)	Bronchial inflammation, malaria fever, conjunctivitis, gastro-intestinal disturbance, enteritis /anti-malarial,spasmolitic, sedative, hypotensive anti-inflammatory	[119]
41. *Melissa officinalis* (Balm)	Antispasmodic, carminative, against migraine and rheumatism / antitumor, anti-inflammatory, neuroprotective	[120, 121]

	anti-inflammatory, hypoglycemic	
42. *Mentha piperita* (Mint)	Antitumor, antiallergenic, hemopreventive, anti- inflammatory	[122, 123]
43. *Monodora myristica* (Calabash nutmeg)	Stimulants, stomachic, for headaches, sores /cardiac, antihypertensive, anti-inflammatory anti-diabetic, hepatoprotective	[124, 125]
44. *Murraya koenigii* (Curry leaf)	Skin diseases, neurosis, stimulate digestion, / antidiabetic, hypocholesterolemic antiulcer, analgesic, antinociceptive, radioprotective, chemoprotective	[126]
45. *Myristica fragrans* (Nutmeg)	Carminative, astrigent, aphrodisiac antiinflammatory, antithrombotic, anti-diarrheal, stomachic /anticancer, antidiabetic, antiobesity	[127, 128]
46. *Myrtus communis* (Myrtle)	Diarrhea, peptic ulcer, hemorrhoids, pulmonary and skin diseases /anticancer, hepatoprotective, anti-genotoxicity, neuroprotective activity	[129, 130]
47. *Nigella sativa* (Black caraway)	Carminative, aromatic, stimulant, diuretic anthelmintic, galactagogue and diaphoretic / hepatoprotective, antidiabetic, anti-inflammatory cytotoxic, anthelmintic, analgesic, anti-cancer, anti-diabetic, anti-hypertensive	[131, 132, 133]
48. *Ocimum basilicum* (Basil)	Digestion, and nervous system/ anti-ulcerogenic, anti-inflammatory antispasmodic, carminative, diaphoretic, digestive, stomachic	[19, 134]
49. *Olea europaea* (Olive)	Hemorrhages, fevers, reduce LDL cholesterol and blood pressure levels, anti-inflammatory	[135, 136]
50. *Origanum vulgare* (Oregano)	Coughs, asthma, croup, bronchitis rheumatoid arthritis, urinary infections, headaches	[137]
51. *Origanum majorana* (Marjoram)	Asthma, stomach pain, headache/anticancer	[138, 139]
52. *Pandanus amaryllifolius* (Pandan leaves)	Strengthen nerve (tonic), increase of appetite reduce fever, solves skin problems/ antioxidant, anticancer	[140, 141]
53. *Petroselinum crispum* (Parsley)	Carminative, tonic and digestive diuretic/immunosuppressant, treatment of hyperuricemia	[142, 143]
54. *Persicaria odorata* (Vietnamese coriander)	Lung and stomach injuries, feverish coughs anti-inflammatory, antitumor	[101]
55. *Pimpinella anisum* (Anise)	Digestive, carminative / insecticidal, antidiabetic	[144]
56. *Piper capense* (Timiz)	Abdominal disorders, bacterial skin infections and polio/ anticancer	[145]
57. *Piper guineense* (Ashanti pepper)	Anti rheumatism, hepatoprotective/ antihelmintic	[146]
58. *Piper nigrum* (Black peper)	Gastro-protective, antidepressant, / Anti-inflammatory, antimutagenic, anti-metastatic antitumor, hepatoprotective	[19,147, 148]
59. *Piper retrofractum* (Long pepper)	Stomach distension or flatulence, dyspepsia, colic, neurasthenia, rheumatism, bronchitis/ neurotrophic, anticancer	[150, 151]
60. *Polygonum hydropiper* (Water-pepper)	Diuretic and emmenagogue. regulate menstrual irregularities against cancer, treating headache, pain, toothache, liver enlargement, gastric ulcer/ antioxidant, antimicrobial antihelminth, antifeedant, cytotoxic, anti-inflammatory, antinociceptive	[151]
61. *Rhus coriaria* (Shumac)	Diarhea, dysentery, ulcer, hemorrhoids, hemorhage, wound healing, hematemesis, leucorhea, sore throat, ophthalmia, non-mutagenic, chondroprotective, antimicrobial, conjunctivitis/ DNA protective	[152]
62. *Rosmarinus officinalis* (Rosemary)	Digestion problems, liver and gallbladder complaint for cough, headache, high blood pressure, antidiabetic, reducing age-related memory loss/anti-Alzheimer,anticancer	[153,154]
63. *Ruta graveolens* (Rue)	Ligaments, tendons, varicose veins and eyesight treatment / anti-inflammatory, antihyperglycemic, anticancer	[155, 156]
64. *Salvia officinalis* (Sage)	Antihydrotic, antispasmodic, astringent, carminative, cholagogue, galactofuge, stimulant, tonic and vasodilator /antidiabetic, antitumor, anti-inflammatory, against neurodegenerative disease	[16, 157, 158, 159]
65. *Sanguisorba minor* (Salad burnet)	Used to stop internal bleeding and hemorrhages, prevent or ameliorate Alzheimer's disease/anticancer	[160]

66. *Satureja hortensis* (Summer savory)	antiseptic, inhibitory effect on oxidative DNA damage	[161]
67. *Satureja montana* (Winter savoiry)	Antiseptic, carminative, digestive, expectorant, stomachic/ cytotoxic,	[162, 163]
68. *Schinus terebinthifolius* (Brazilian pepper)	Antipyretic, analgesic, depurative anti-inflammatory, antitumor, antiulcerogenic	[164, 165]
69. *Sesamum indicum* (Sesame)	anti-carries, hypoglycemic, antitumor, hepatoprotective	[166, 167]
70. *Sinapis alba* (White mustard)	Analgesic, carminative, expectorant, chronic bronchitis rheumatism, muscular and skeletal pains/ anticancer,	[168]
71. *Smyrnium olusatrum* (Wild celery)	Asthma, menstrual problems, wounds/anticancer	[169]
72. *Syzygium aromaticum* (Clove)	Headache, nausea, toothache, hypertension sore gums/anticancer, anti-inflammatory	[170, 171]
73. *Tagetes minuta* (Huacatay)	Relieve flatulence, improve appetite /anti-inflammatory, bronchodilatory, hypotensive, spasmolytic	[172, 173]
74. *Tasmannia lanceolata* (Tasmanian pepper)	anticancer, to treat cardiovasculr diseases, antiallergic, anti-inflammatory	[174]
75. *Thymus vulgaris* (Thyme)	Intestinal, bronchial, pulmonary, urinary infections /antiseptic, antispasmodic astringent, anthelmintic, anti-inflammatory, immunomodulatory	[175, 176]
76. *Thymus serpyllum* (Breckland thyme)	Whooping cough, catarrh, sore throat / antitumor, cytotoxis	[177, 178]
77. *Trigonella foenum-graecum* (Fenugreek)	Brain and nervous system ailments, metabolic disorders, / antidiabetic, anticancer,	[179, 180]
78. *Trachyspermum ammi* (Ajwan)	Stomach disorders, for relieving colic pains asthma, dyspepsia, spasmodic disorder flatulence, common cold, acute pharyngitis, /antimicrobial, anticancer	[181, 182]
79. *Vanilla planifolia* (Vanilla)	Dysmenorrhea, fever, hysteria, prevent dental caries, dyspepsia antimicrobial, anticlastogenic, anticarcinogenic, antimutagenic	[183]
80. *Verbena officinalis* (Vervain)	Asthma, used for depression, hysteria, gallbladder pain arthritis, gout, metabolic disorders, /antimicrobial, anticancer,	[184, 185]
81. *Xylopia aethiopica* (Grains of Selim)	Stomach aches, bronchitis, dysentery, headaches and neuralgia /cytotoxic	[186, 187]
82. *Zanthoxylum bungeanum* (Chinese prickly ash)	Anaesthetic, anthelmintic, astringent, carminative, diuretic anti-thrombotic	[188, 189]
83. *Zanthoxylum piperitum* (Japanese pepper)	To healing vomiting, diarrhoea, abdominal pain hepatoprotective, anticancer	[190, 191]
84. *Zingiber officinale* (Ginger)	Anti-inflammatory, anticancer, anti-proliferative, neuro protective rheumatoid arthritis	[18, 192, 193, 194, 195]