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A STUDY OF THE IMMUNOMODULATORY EFFECT OF COMMONLY USED SPICES IN SRI LANKA

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ABSTRACT

A robust immune system reduces harm to the body and protects the body from pandemic infections. Spices are essential components of the diet. And possess anti-inflammatory, antioxidant, immunomodulatory activities and antiviral properties. Cinnamomum zeylanicum (CZ), Piper nigrum (PN), Syzygium aromaticum (SA), Elettaria cardamomum (EC), Myristica fragrant (MF), Curcuma long (CL) are the spices selected for this study. Aim: To determine the effect of cytokines and antioxidants on the immunomodulatory effect. Methodology: Research was done as systematic literature following the PRISMA model. Results: the main phytochemicals of CZ, PN, SA, and EC are Cinnamaldehyde, piperin, Eugenol, and 1,8-cineole, respectively. MF contains meso-dihydroguaiaretic acid, myristicin, and malabaricone and CL – turmerone and curcumin. Cinnamaldehyde increases IL-1β, IL-6, IL-15, and IFN-γ, PN increase the Th1 (T helper cell type 1) cytokines level ((IL-1β, TNF-α, IL-12), SA increase Th2 cytokines (IL-4, IL-10, and TGF-β). EC reduced the proliferation of the splenocytes, IL-2, IL-4, and IFN-γ inhibit by MF. CL increase the IgA, IgG, and IgM levels. DPPH, β-Carotene-linoleic acid bleaching test, FRAP method are used for test for antioxidant effect. Results were positive. IFN-γ promotes pro-inflammatory cytokines, IgA, IgG, and IgM significantly improve the autoimmune diseases, IL-4 helps to T cells to convert Th2 cells, IL-2 and lymphokine delay replace of Reactive Oxygen Species (ROS) which attack the immune system. Therefore, need an adequate level of antioxidants to protect the body from diseases. All the spices mentioned above have a significant immunomodulatory and antioxidant effect against diseases.

Key words: Spices, Immunomodulatory activity, Natural antioxidants, Cytokines

INTRODUCTION

Despite globalization, people in Asian countries are still the largest consumers of spices. Spicy food does not only provide an important hedonic input in daily life, but has also been anecdotally associated to beneficial effects on our health. Despite considerable advances over the years in elucidating the underlying mechanisms, the present knowledge of the beneficial effects of spices are far from sufficient. While chemical structures of some of the bioactive components from several of these compounds have been identified, there are likely more components that have either not been identified or tested for their bioactive role. Spices have been used for centuries in various parts of the world for food coloring, flavoring, and preserving as well as many applications in nutrition and medicine. They have been derived from various parts such as leaves,

flowers, fruits, buds, bark, and roots also and has many uses like anti-inflammatory, antiviral, antimicrobial, antibacterial, antifungal, wound-healing, anti-mutagenic and even anticancer effect. Although the prevalence of herbs and spices is extensive globally, preclinical and clinical research have been elaborated on their effectiveness in health promotion only in recent years.

Main spices are added for the main dishes in sri lanka. Some of them are Cinnamon- Cinnamomum zeylanicum (CZ), Pepper -Piper nigrum (PN), Clove - Syzygium aromaticum (SA), Cardamom - Elettaria cardamomum (EC), Nutmeg - Myristica fragrant (MF), Turmeric - Curcuma long (CL). Healthy life patterns and healthy food behaviors reduce the accumulation of unwanted things in the body and enhance the immunity. People believe a healthy diet makes the body strong against pathogens. WHO have been confirmed 646,266,987 cases of COVID-19, including 6,636,278 deaths. HIV/AIDS has also proven a global pandemic killing more than 36 million people. Millions of people were victimized by other pandemics like flu, cholera, smallpox. For the achievement of the pandemic situation, good immunity of the persons is very important to attacks pathogens and protect the body.

The immune system is an organization of cells and molecules. The innate (natural) and acquired(adaptive) response are two different fundamentals that respond to infectious agents. Monocytes, macrophages, neutrophils, and cytokines like inflammatory mediators were used for the innate immune system. (Delves et al, 2000) Immune modulatory drugs respond to the immune system by increasing the production of serum antibodies and bring remarkable progress in conditions such as cancers, AIDS, and autoimmune diseases. The immune system is built up with the roles of T and B cells, macrophages, and phagocytes with the special attention of cytokines (Takx-Köhlen, 1992).

Cytokines are extracellular proteins and act as intracellular regulators and mobilizers. these proteins primarily act as antiviral and antineoplastic agents. according to some studies they are now responsible for innate and adaptive inflammation (Spelman et al., 2006). Cytokines have involved the communication between T cells and macrophages. macrophages were produced especially, interferons (IFNs), TNF-α, IL-10, and IL-12. T cells were produced IFNs, IL-2, IL-4, IL-10, IL-13 and TGF-β. IFN-α effects to generate Th (T helper cell) type 1 which response to human diseases like early AIDS, hyper-eosinophilia, and certain tumors (Belardelli, 1995). Immune system cells were active by the cytokines and they respond to cancer too (Mocellin et al., 2001). Th type 1 includes IFN-γ and IL-2 these cytokines are contributed to activating macrophages. They help to digest external microbes and helps to secrete other types of cytokines that activate acute inflammation such as IL-6, and TNF-α. IL-12. They stimulates to release of IFN-γ which helps to release TNF-α and reactive oxygen and nitrogen radicals (Sharma et al., 2001).

Free radicals play a major role in the body. Accumulation of polyunsaturated fatty acids and free radicals mediate the lipo-peroxidase of the cell membrane. It will lead to reduce fluid content inside the cells. Many protective functions of the immune system are dependent on the fluidity of the cells. Decrement of fluid content will reduce the ability of the lymphocytes to respond against pathogens. It will consequently increase the risk of infections and the development of certain cancers. (Bendich, 1993).

This article provides a systematic review of the immunomodulatory effect of the above spices in addition to the therapeutic purpose.

Objectives

General objectives

Scientific review of immunomodulatory effect of commonly use select spices in sri lanka.

Specific objective

To identify the most effective phytochemical of selected spices

To identify the effective cytokines for immune modulatory.

To identify the antioxidant effect of the selected spices.

METHODOLOGY

A systematic review of published studies reporting the immunomodulatory effect of commonly used spices in Sri Lanka was undertaken in accordance with PRISMA (preferred reporting items of a systematic review and meta-analysis) model (Hébert et al., 2003). Google scholar and Pub-Med used to search articles and the results were limited to English articles, otherwise non-English research, and veterinary articles were excluded.

Total articles which similar to the above criteria were gathered together and duplicate articles were removed. The remaining pool of articles were screened by reading the title and abstract, by identifying the exclusion criteria of some articles were excluded. Remaining articles were screened by reading the full text and those according to the inclusion criteria were included others were excluded. The accepted pool of articles was reviewed by an iterative consensus process.

RESULTS

Literature search

Among 109 total research articles, 36 numbers of articles were found after removing duplications for the present review. By following the above search criteria, the search strategy is summarized in Figure 1

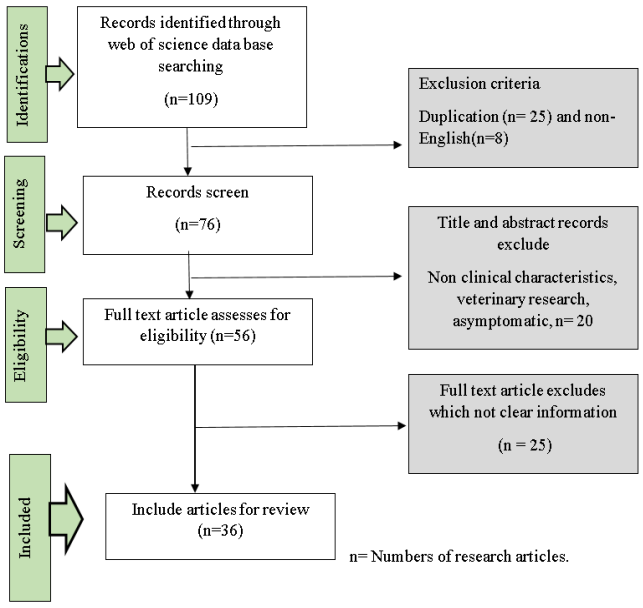

Figure 1 - Summarized search strategy

Review of Phytochemicals of the spices

Cinnamon: Cinnamaldehyde and camphor (Figure- 2) were mainly found in the stem and stem bark of the CZ, major phytochemicals of the other parts were Trans-cinnamyl acetate in flowers and fruit stalks, eugenol in the essential oils from the leaf. (Jayaprakasha et al., 2011) The same array of hydrocarbons in varying proportions of CZ contained in various parts like eugenol from leaf, cinnamaldehyde from bark and root contained camphor (Ranasinghe, et al., 2013). Trans-cinnamaldehyde is a main phytochemical found in the bark essential oils (49.9–62.8%). (Singh et al., 2007), essential oil of the CZ found phytochemicals such as 68.95% of Cinnamaldehyde, 9.94% benzaldehyde, and 7.44% cinnamyl acetate (Unlu, et al., 2010).

Pepper: The main phytochemical of the PN was piperin (Figure- 2). It was the first phytochemical can easily isolate from the Piperaceae family. Other phytochemicals were Dihydro-pipericide, (2E,4E)-N-Eicosadienoyl-pereridine, N-trans-Feruloyltryamine, N-Formylpiperidine, Guineensine, pentadienoyl as piperidine, (2E,4E)- Nisobuty- ldecadienamid, isobutyl-eicosadienamide, Tricholein, Trichostachine, isobutyl-eicosatrienamide, Isobutyl-octadienamide, Piperamide, Piperamine, Piperettine, Pipericide, Piperine, Piperolein B, Sarmentine, Sarmentosine, Retrofractamide mentioned by Delves et al., 2000. β-caryophyllene (16.0 %), sabinene (12.6 %), limonene (11.9 %), and torreyol (9.3 %) were the phytochemicals identified in the essential oil of the PN. It have significant ability to inhibit fungus like Penicillium viridicatum and Fusarium graminearum. (Singh et al., 2013).

Clove: The main components of the Syzygium aromaticum (SA) were eugenol (78.67%) (Figure- 2), eugenol acetate (11.77%), and caryophyllene (6.85%). HPLC (High-performance liquid chromatography) analysis had given the results of the percent of gallic acid, rutin, and quercetin like phytochemicals. Aqueous and ethanol extract of SA presents effective immunomodulatory activity by inhibiting neutrophil bacterial activity (El Faqer et al., 2022). Chemical composition of the SA leaf extract was analyzed by using the GC-MS method and the results were 74.28% eugenol, 5.78% eucalyptol, 3.85% caryophyllene, 2.43% α-cardinol and 2.08% limonene (Bhuiyan et al., 2010).

Cardamom: The TLC method shows a high amount of 1,8-cineole (45.6%) in Elettaria cardamomum (EC). Terpinyl acetate (33.7%), sabinene (3.8%), 4-terpinen-4-ol (2.4%), and myrcene (2.2%) were the other phytochemicals (Masoumi et al., 2016). Essential oil of the EC has strong antibacterial effect on Staphylococcus aureus, Bacillus cereus, Escherichia coli, and Salmonella typhi, and an antifungal effect on Aspergillus terreus, Penicillium purpurogenum, Fusarium graminearum and Penicillium madriti. (Singh et al., 2008). 1,8-cineole (25.6%), linalool (6.3%), and αterpinyl acetate (40.7%) are the major components were reported by (Savan et al., 2013).

Nutmeg: meso-dihydroguaiaretic acid, myristicin (Figure- 2), and malabaricone are the main phytochemicals (Ha et al., 2020). Lignans, neolignans, diphenylalkanes, phenylpropanoids, terpenoids Trimyristin, myristic acid, myristicin, safrole, and elimicin were the components reported from MF which have remarkable biological activity (Asgarpanah et al., 2012). Terpinen-4-ol, β-pinene, and limonene were percent in the essential oil of the MF (Kuete et al., 2017).

Turmeric: Fresh Curcuma longa (CL) contained alpha-turmerone (53.4%) as the major component other chemicals were beta-turmerone (18.1%) and aromatic-turmerone (6.2%). Aromatic-turmerone (9.6%), alpha-santalene (7.8%), and

alpha-turmerone (6.5%) were found on the dry rhizome respectively. High amounts of alpha-turmerone were found in the fresh rhizomes and it was the minor component in the dry rhizomes (Singh et al., 2013). Primarily phenolic and terpenoids were found from the CL. Curcuminoids (Figure- 2) and sesquiterpenes are accumulated in the rhizome as primary chemicals (Li et al., 2011).

The table 1 demonstrated the detailed account of active compounds in the spices commonly used in Sri Lankan cuisine.

Table 1 - Active compounds of the spices commonly used in Sri Lanka (Source: https://pubchem.ncbi.nlm.nih.gov/compound)

Name of the spice & Scientific Name	Description		
	Component/s	Active Compound/s	Chemical Formula
Cinnamon *Cinnamomum verum* or *Cinnamomum zeylanicum*	Bark	Cinnamaldehyde - Melting point: -7.5 °C and Molar mass: 132.16g/mol	C_9H_8O
	Leaf	Eugenol - Melting point: -7.5 °C and Molar mass: 164.2 g/mol	$C_{10}H_{12}O_2$
	Root	Camphor - Molar mass: 152.23 g/mol and Melting point: 175 °C	$C_{10}H_{16}O$
Turmeric *Curcuma longa L.*	Rhizomes	Curcumin - Molar mass: 368.38 g/mol and Melting point: 183 °C	$C_{21}H_{20}O_6$
Clove *Syzygium aromaticum L.*	Flower buds	Euginol - Molar mass: 164.2 g/mol and Density: 1.06 g/cm³	$C_{10}H_{12}O_2$
Cardamom *Elettaria cardamomum*	Pods	Protocatechualdehyde - Molar mass: 138.12 g/mol	$C_7H_6O_3$
		Alpha-terpinyl acetate	CH_{20}
		a-terpineol - Molar mass:154.25 g/mol and Melting point: −35. 9−28.2°C	$C_{10}H_{18}O$
Nutmeg and Mace *Myristica fragrans Houtt*	Seed - nutmeg, mace	Myristicin	$C_{11}H_{12}O_3$
		Eugenol	$C_{10}H_{12}O_2$
		Methylisoeugenol	$C_{11}H_{14}O_2$
Black pepper *Piper nigrum L.*	Seeds	Piperine - Molar mass: 285.34 g/mol and Melting point: 130°C	$C_{17}H_{19}NO_3$

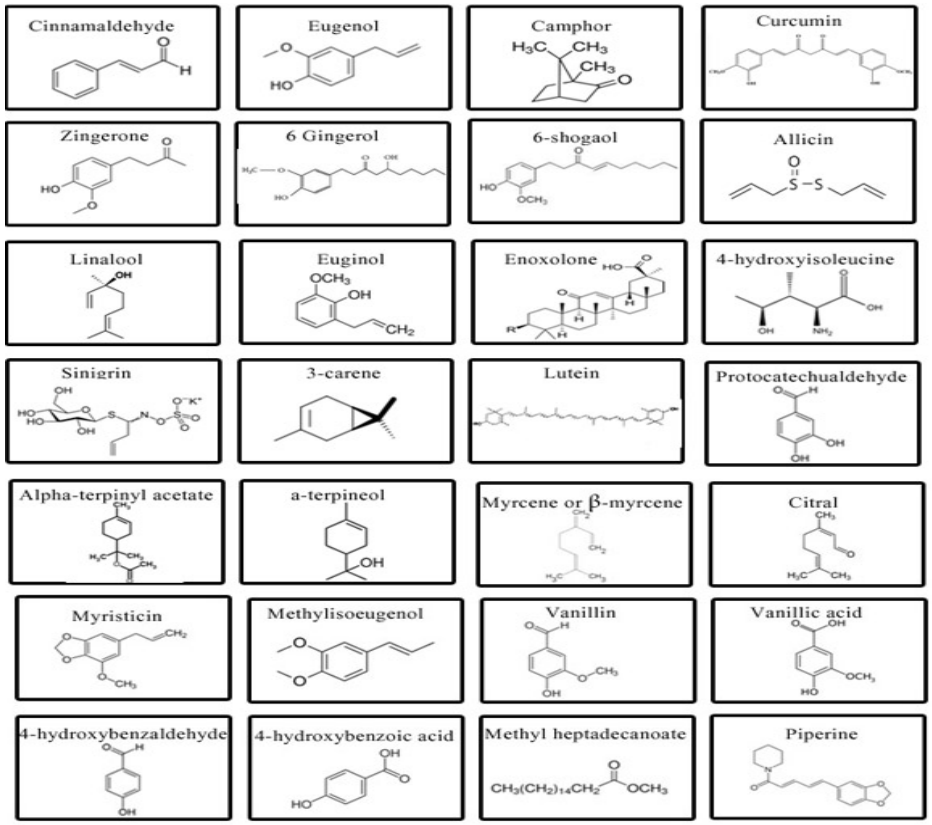

Figure 02: Chemical Structures of the active compounds of the spices used in Sri Lanka (Source: https://pubchem.ncbi.nlm.nih.gov/compound)

Review of immune modulatory effect.

Cinnamon: Very least amount of research was found on in vitro studies of the immunomodulatory effect of CL. Some research was done on mice lethality tests. Cinnamon bark increased serum immunoglobulin levels, and increase neutrophil adhesion. Cinnamaldehyde increases IL-1β, IL-6, IL-15, and IFN-γ and has an effect of inhibiting lymphoproliferative and induced T-cell differentiation and has no effect to increase the production of IL-2. It will respond to blocked early steps of the signaling pathway of cell growth (Koh et al., 1998). In vivo studies of CZ reported cinnamon bark extract has an effect of increasing the amount of hemoglobin, white blood cells, lymphocytes and immunoglobulin level in the blood and enhance the phagocytic activity (Niphade et al., 2009) (Huang et al., 2018).

Pepper: Piperine is the major compound found in the PN (Delves et al., 2000). It helps to increase the white blood cell count, born marrow cellularity, and alpha-esterase positive cells. In vivo experiments of PN reported an increase of the Th-1 cytokines (IFN-γ and IL-2), a proliferation of T and B cells, and increased macrophage activation (Damanhouri et al., 2014). Piperine has the effect of increasing the cytokines level of IL-1β, TNF-α, and IL-4 (Ferreira et al., 2020) has a high possibility of binding CD4 and CD8 receptors (Kumar et al., 2015). Other than helps to increase the Th1 (T helper cell type 1) cytokines level ((IL-1β, TNF-α,

IL-12) and decrease the Th2 (T helper cell type 2) cytokines level (IL-4, IL-10) (Santos et al., 2013).

Clove: Ethanolic extracted Syzygium aromaticum (SA) has the effect of increasing tumor necrosis factor TNF-α, interleukin IL-6, and IL-12 (Dibazar et al., 2015), (Mahapatra et al., 2011). Clove increase the B cell expansion and decrease the T cell proliferation and suppress the Th1 cytokines (IFN-γ) and support to enhance the Th2 cytokines (IL-4, IL-10, and TGF-β). (Dibazar et al., 2014), (Mahapatra et al., 2011).

Cardamom: Fresh nutmeg cardamom suppresses the cytokines of Th1 and enhances the Th2 cytokines (Majdalawieh et al., 2010). Nitric oxide production of the macrophages was inhibited by EC. Immunomodulatory activity of the splenocytes was analyzed by using EC and the results reduced the proliferation of the splenocytes. It will make a good immunomodulatory effect (Kumar et al., 2021).

Nutmeg: Production of IL-2, IL-4, and IFN-γ inhibit by aril of the fruit of Myristica fragrans MF (Checker et al., 2008) was experimented by using con A treated mammalian splenocytes and the immunomodulatory effect was found by the decreased production of cytokines IL-6 and IL-10 (Babua et al., 2021).

Turmeric: Curcumin was the major phytochemical of CL which is effective to increase the IgA, IgG, and IgM levels in the blood (Huang et al., 2014). Helps to enhance the circulating antibody titer, total WBC count, bone marrow cellularity, α-esterase positive cells in the Curcumin-treated rats.(Antony et al., 1999) and it decreased the secretion of IL-6 (Seyedzadeh et al., 2014).

Review of antioxidant effect

Cinnamon: Following the DPPH method, essential oils of the CZ were present in 50% of IC50 which is calculated by the calibration curve. Another way of finding the antioxidant effect is the β-Carotene-linoleic acid bleaching test which gives positive results. To find out the antioxidant compound of the DPPH sample and β-Carotene-linoleic acid bleaching test using the TLC method compound were colored as pale yellow and orange spots respectively (El-Baroty et al., 2010). Free radical scavenging effect of Cinnamaldehyde was reported as 96.32 % and 96.29 %, respectively in monoamine oxidase (MAO) A and MAO-B inhibition assay. Cinnamaldehyde (83.75 %) and Cinnamyl acetate (45.58 %) percentages were reported effective antioxidant properties under the Tyrosinase inhibition assay. Phosphomolybdenum. (Tepe et al., 2020).

Pepper: According to 1,1′-diphenyl-2-picrylhydrazyl (DPPH) and ferric thiocyanate, Pepper has a significant free radical scavenging effect (Singh et al., 2013). 64.1 μmol/ml α-tocopherol equivalents of piperic acid have a higher antioxidant effect than 58.8 μmol/ml α-tocopherol equivalents of piperine results were analyzed by using phosphomolybdenum assay which quantitatively method to identify antioxidant method. Ethanolic extract of PN has a higher antioxidant effect (Zarai et al., 2013). Antioxidant effect of both water and ethanol extracts of the black pepper (PN) were experimented with by using DPPH, superoxide anion, hydrogen peroxide scavenging, and metal chelating activity with results of strong antioxidant activity. 75 μg/ml concentration of water-extracted black pepper (95.5%)shows the highest free radical scavenging activity than ethanol-extracted black paper(93.3%) under the peroxidation of linoleic acid emulsion (Gülçin., 2005)

Clove: Eugenol (71.56%), eugenol acetate (8.99 %), and thymol (0.87 %) of the SA recorded the highest antioxidant effect which is done by the DPPH method. 400mg/ml concentration of all extract

have remarkable inhibition of the DPPH scavenging effect (Nassar et al., 2007). Clove extracts showed 25.3 to 91.4%, varying of DPPH method and 49.4 to 99.4% of ABTS method (El-Maati et al., 2016). Hexanal and malonaldehyde formation was the method used to identify an antioxidant method of cloves the aroma extract of clove buds inhibited the oxidation of hexanal for 30 days at a level of 50 μg/ml. extract of the Clove bud inhibited malonaldehyde formation from cod liver oil by 93% at the 160 μg/ml level (Lee et al., 2001).

Cardamom: Thiocyanate method is used to identify the antioxidant effect of EC. The result is 84.2-90% inhibit the peroxidation. and according to the DPPH method, 70% of the methanolic extract of EC shows a lowest IC50 value (17.26 μg/mL) which means a higher antioxidant effect (Bhatti et al., 2010). According to the DPPH method methanolic extract of cardamom powder has a significant free radical scavenging effect (Khalaf et al., 2007). EC shows IC50 value 217.432 μg/ml of the DPPH method (Sultana et al., 2010).

Nutmeg: Various extracts of nutmeg MF have been used for the determination of the antioxidant effect of 1 mg/mL of acetone extract, which was reported highest antioxidant effect by using the DPPH method is 63.04 ± 1.29%, and 74.36 ± 1.94% percentage of the highest antioxidant effect is shown by β-Carotene bleaching assay of the same extract. 1.0 mg/mL of ethanol extract has an antioxidant effect (72.11 ± 1.54%,) which is done by Chelation activity on Fe2+ (Gupta et al., 2013).

Turmeric: Ethanolic extract of CL has the highest antioxidant effect than aqueous extracts investigated by the DPPH method. and FRAP method shows effective free radical scavenging activity also (Tanvir et al., 2017). Turmerin (183 nm) 80% protects the DNA and membrane from oxidative injury. Arachidonate and mutagenic activity of t-butyl hydro peroxide were inhibited by turmerin (Srinivas et al., 1992).

DISCUSSION

A detailed examination of the effects of spices & condiments as well as of the extracts or individual purified chemical components will determine not only the beneficial effects but also whether certain components act synergistically or antagonistically to produce an end effect. While it is beneficial to know the overall effect of spices & condiments, it is often difficult to know the contribution of the individual chemical constituents when consumed as spices & condiments. It is important to study the bioactive compounds that can modulate target functions related to defense against oxidative stress, and that might be used to achieve health benefits individually.

The vast number of organisms in the surrounding environment has a high ability to invade the body through the skin, inhaling, and swallowing. The immune system is an interactive system that integrity the host defense mechanism with the help of lymphoid organs, cells, humoral factors, and cytokines, protecting the body from unwanted pathogens (Parkin et al., 2001). Various kinds of foods have the effect of antioxidant, anti-inflammatory, and immunomodulatory activities according to the evidence of the results of the experiment selected spices have an effective immune modulatory effect.

Natural therapy makes a diverse array of today's world. Phytochemicals are naturally occurring bioactive potentials which have immuno-stimulating activity (Brindha., 2016). The main phytochemical of cinnamon (CZ) is Cinnamaldehyde which can be seen in the bark essential oil (Ranasinghe et al., 2013) significant antimicrobial effect of the essential of CZ were found by some

experiments in vitro assay of essential oils were reported strong cytotoxicity with IC50 values (Unlu et al., 2010).

IL-2 and lymphokine-activated killer cells represent non-cross-resistance therapeutic modality that delay replaces. To determine the safety tolerance of IL-2 therapy in vivo experiments done for acute leukemia, lymphoma, or multiple myeloma patients and they were exhibited mild to moderate fever, diarrhea, and skin rashes like complications with IL-2 infusions were reported by (Higuchi et al., 1991). CZ and MF have the effect of inhibiting the production of IL-2 and helping to reduce toxicity.

CZ bark extract has the effect of increasing the serum immunoglobulin (IG) level. Other than CL support to increase the IgA, IgG, and IgM (Huang et al., 2014). Significant improvements of autoimmune diseases were reported with the help of clinical trial series and case reports. IG has antimetastatic activity in cancer cells and effect for recurrent pregnancy loss. IG has the ability to neutralize pathogenic autoantibodies and helps the induction of IL-12 secretion, which consequently activates natural killer cells and increase the proapoptotic genes in cancer cells (Sapir et al., 2005).

IFN-γ promotes pro-inflammatory cytokines which enhance the binding of macrophages and T cells and increase the response to inflammatory diseases by modulating anti-inflammatory factors. IFN-γ involves in macrophage polarization to M1 and M2. M2 facilitates tissue repairing M1 supply pathological effect for secretion of pro-inflammatory cytokines (Jiang et al., 2013). Piperine of the PN has the ability to increase the IFN-γ (Damanhouri et al., 2014)

IL-6 has an antiinflammation effect, immune response and has the effect of hematopoietic. It promotes the mega megakaryocyte maturation and increases the release of platelets. MF, and SA increasing the secretion of IL-6 (Tanaka et al., 2014).

IL-4 helps to T cells to convert Th2 cells which help to B cells and promote the production of IgM to Ig G1 and Ig E (Choi et al., 1998). PN, SA, and MF has the effect of increased IL-4.

The particularly therapeutic effect of IL-10 is control of the antigens of the intestine against inflammatory diseases. And store the resident intestinal bacteria (Steidler et al., 2000). were Reported by the evidance based on clinical trial of inflammatory bowel diseass patients (Van Deventer et al., 1997) (Lammers et al., 2003).

P N (Damanhouri et al., 2014) and CL (Antony et al., 1999) have an effect to increase bone marrow cellularity. cancer treatments change the distribution of the hematopoietic (red) and fatty (yellow) marrow and increase the yellow marrow more than the red marrow. It will affect the host defense mechanism. PN and CL help to build up a strong immune system by increasing bone marrow cellularity.

Reactive oxygen species (ROS) and free radicals contribute to many diseases and aging (Arulselvan et al., 2016). Within a hypoxic situation, mitochondria produced NO and will lead to produced reactive nitrogen species and which produced other additional excessive lipid peroxidation and alteration of the mutagenic process (Victor et al., 2014). EC has the effect of NO production inhibition. (Kumar et al., 2021) and prevent the harmful effect from NO. All the spices were experimented with free radical scavenging activity by using standard measurements of the antioxidant effect.

In vivo and in vitro experiments of the above-mentioned spices have effective free radical scavenging activity. Reactive oxygenase stealing electrons from closet stable molecules attacked molecules and become free radicals by losing electrons. Causing damage to the living cells

(Arulselvan et al., 2016). ROS attacked the immune system and reduced the ability to face harmful pathogens. Immune cells use ROS to support their functions and therefore need an adequate level of antioxidants to protect the body from diseases (Victor et al., 2014). In ordinary and healthy body condition, there is a balance between ROS formation/free radical and endogenous antioxidant defense mechanisms. However, if this equilibrium is concerned, it can lead to oxidative stress and associated damage. This oxidative stress condition can cause injury to all vital cellular components such as DNA, proteins, and membrane lipids and it may lead to cell death. This inflammatory/oxidative environment triggers an unhealthy circle, which can harm healthy stromal cells and neighboring epithelial cells, which after a long period of time may trigger carcinogenesis.

These active compounds can stimulate signal transduction cascades in addition to alterations in transcription factors, like nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3, activator protein1, NF-E2 related factor-2, nuclear factor of activated T cells, and hypoxia-inducible factor-1α (HIF1-α), which mediate vital cellular stress reactions. Beginning of cyclooxygenase-2 (COX-2), inducibility of nitric oxide synthase (iNOS), and high expression of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and chemokines (CXC chemokine receptor 4), in addition to fluctuations in the expression of specific microRNAs, have also been exhibited to have a role in oxidative stress-induced inflammation.

The inflammatory cytokine reaction is only one molecular response signal and trackable biomarker to determine the health of the body's immune system, and many other factors of relevance to the body's immune response. In inflammatory response, leukocytes and mast cells are present in the damage regions which direct to a "respiratory burst" as a result of an enhanced uptake of oxygen and therefore enhance the production and release of ROS at the damaged area. However, inflammatory cells generate more soluble inflammatory mediators such as cytokines, arachidonic acid, and chemokines, which act through active inflammatory cells in the area of infection and release more reactive species. In the present review, an attempt has been made to summarize the most current scientific evidence about the in vitro and in vivo effects of the bioactive compounds derived from spices with a focus on immune enhancing effect

in order to provide science-based evidence for traditional uses and develop either functional foods or nutraceuticals.

CONCLUSION AND SUGGESTIONS

Spices used in Sri Lanka and India exhibit a wide range of physiological and pharmacological properties. The immunomodulatory effect is the most valuable thing for the human body. All the spices mentioned in this article contributed to increasing immunology in various ways. Cinnamomum zeylanicum , Piper nigrum , and Myristica fragrant reduced the production of IL-2 and prevent the body from toxicity. Piper nigrum and Curcuma long increase bone marrow cellularity which produced RBC, WBC, and lymphocytes. Immunoglobulin which protects the body from autoimmune disease is increased by the Cinnamomum zeylanicum and Curcuma long. Other interleukins IL-6, IL-4. IL-10 which stimulates the activity of the macrophages is increased by Cinnamomum zeylanicum , Syzygium aromaticum , Elettaria cardamomum , Piper nigrum , Myristica fragrant , and Curcuma long. Different

ways of contributing spices are a valuable gift from nature. This review will help with drug development from natural herbals. Suggest doing clinical trials for further studies and laboratory experiments to find out the phytochemicals aqueous extracts of these spices further studies.

ABBREVIATIONS

Table 2- abbreviations list

CL	*Curcuma longa*
CZ	*Cinnamomum zeylanicum*
DPPH	2,2-diphenyl-1-picryl-hydrazyl-hydrate
EC	*Elettaria cardamomum*
GC- MS	Gas chromatography–mass spectrometry
IFN-γ	Interferon gamma
IG	Immunoglobulins
IL	Interleukins
TNF-α	Tumor necrosis factor alpha
MF	*Myristica fragrant*
NO	Nitric oxide
PN	*Piper nigrum*
TLC	Thin layer chromatography
SA	*Syzygium aromaticum*

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