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MINI REVIEW

Bioactive Compounds in Anti-Inflammatory Prevention

Joanna Soin *

Institute of Health Sciences, Stefan Batory State University, Skierniewice, Poland

Abstract

Spices and flavorings have been used as food since ancient times and also as medicines and food preservatives in recent decades. Many spices-such as clove, oregano, thyme, cinnamon, and cumin-have been used to treat infectious diseases or to protect food. They have been proven to have antimicrobial activity against pathogenic fungi and bacteria. Furthermore, secondary metabolites of these spices are known as antimicrobial agents, most of which are considered safe with minimal side effects.

Therefore, spices may be candidates for the discovery and development of new agents against foodborne and human pathogens.

A century ago, during the Spanish flu pandemic (1918-1919), the saying arose: "whoever has sage in the garden, has health in his body!"

In addition to antibacterial and antiviral properties, herbs and spices also contain many bioactive compounds with anti-inflammatory and anticancer properties. Bioactive substances in the diet may also affect the structure of DNA or gene expression. Substances affecting the expression of genes. - short chain fatty acids or group of compounds involved in methylation of DNA strands. Such a diet should not miss the vegetable products rich in compounds having a stimulating effect on the immune system which is directly connected with the control of the anticancer properties [55].

Our own research has shown that Fucoidan - a vegetal sulfated polysaccharide extracted from the brown seaweed - is able to improve vascular remodeling process triggered by immunological stimuli in rat allogenic aorta transplantation model, as well as evaluated potential mechanisms responsible for the observed effects [56].

***Corresponding author(s)**

Joanna Soin, Institute of Health Sciences, Stefan Batory State University, Skierniewice, Poland

Tel: +486-677-12896
Email: jsoin@ansb.pl

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- Bioactive compounds
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- Virus
- Antiviral activity
- Essential oil

Summary

Spices and aromas have been used as food since ancient times, as well as as medicines and food preservatives. Many spices - such as clove, oregano, thyme, cinnamon and cumin - have been used to treat infectious diseases or to protect food. Same of them contain phytochemicals like - quercitin - as a reverse transcriptase inhibitor provides anti-viral effects on all RNA viruses, another one contains bioactive compounds like polyphenoles - due to inactivation of free radicals species or essential oil.

Introduction

Spices and aromas have been used as food since ancient times [1], as well as as medicines and food preservatives [2,3]. Many spices - such as clove, oregano, thyme, cinnamon and cumin - have been used to treat infectious diseases or to preserve food. They have been proven to have antimicrobial activity against pathogenic fungi and bacteria [1,4,5]. In addition, the

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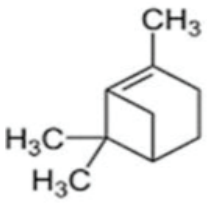
secondary metabolites of these spices are known as antimicrobials, mostly considered as safe or having only minor side effects [2]. Therefore, spices may be candidates for discovery and development of new agents against food and human pathogens [6].

One hundred years ago, during a Spanish flu pandemic (1918-1919), a saying was coined that stated, "whoever has sage in the garden, has health in his body!"

SAGE/Salvia

Sage contains substances that have antiviral and antibacterial properties. Sage eliminates infections, but also strengthens the immune system. It captures free radicals, i.e. has antioxidant effects. Its main bioactive compounds are: polyphenols and essential oils, i.a. thujone, cineol, borneol and pinene (Figure 1).

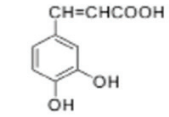


α-pinen

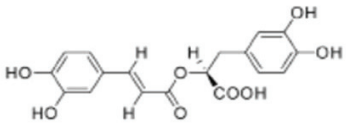
Sage/*Salvia*

The aqueous and ethanol extracts of Salvia officinalis and Salvia coccinia show important antiviral activity against HSV-1 and HSV-2 [7,8]. Santoyo S, et al. [9] demonstrated the antiviral properties of supercritical CO2 extracts obtained from oregano and sage. They were evaluated for herpes simplex virus type 1 at various stages of virus infection. All tested extracts showed moderate direct virucidal activity. In addition, supercritical extracts of sage and oregano were able to significantly inhibit virus replication *in vitro*, showing IC50 values of 1.88 and 5.33 µg / ml, respectively. Compounds responsible for the antiviral activity found in supercritical sage extracts were identified as : borneol, camphor and 1,8-cineol.

Studies have shown that some biological properties of sage essential oil are based on camphor. Sage essential oil contains about 20% camphor, and when the leaves expand, the camphor content also increases. Other bioactive compounds found in sage are: sage acid, rosmarinic acid, carnosolic acid, caffeic acid, etc. [10-12] (Figure 2).



Caffeic acid



Rosmarinic acid

Most phenolic acids in Salvia species are derivatives of caffeic acid, which is the building block of various plant metabolites. Caffeic acid plays a key role in the biochemistry of Lamiaceae plants and occurs mainly in the form of dimer as rosmarinic acid [13].

Turmeric

Widely conducted research shows anti-inflammatory, antioxidant and anti-cancer effects of turmeric. Its antibacterial, antiviral and antifungal effects are also reported. Turmeric-related ginger contains curcumin, which has a broad spectrum of action against these pathogens. Curcumin's beneficial effects are partly explained by the fact that it interacts with many compounds, including proteins, enzymes, cytokines, transcription factors and growth factors.Curcumin has been extensively studied for its pleiotropic effects, including anti-inflammatory, antioxidant and anti-tumor effects. Accumulated evidence indicates that curcumin plays an inhibitory role against infection coused by many viruses, including HIV, influenza (PR8, H1N1, H6N1), Parainfluenza type 3 (PIV-3), HSV-1 and HSV-2, coxsackie, HBV, HCV, HPV, JEV, HTLV-1, FIPV, FHV, VSV or RSV. These mechanisms include either direct interference with viral replication or suppression of cellular signaling pathways necessary for viral replication, such as PI3K / Akt, NF-κB. Proteins whose expression is regulated by NF-κB include, i.a. inflammatory cytokines (IL-1, IL-2, IL-6, IL-8), interferons, adhesion molecules (ICAM-1, VCAM-1) and some enzymes. Thus, inhibition of NF-κB activity reduces the expression of genes responsible for the formation of proteins involved in the inflammatory process [14].

Curcumin has a suppressive effect on intercellular signaling cascades that condition effective viral replication. Viruses, in order to ensure their survival, which can be obtained mainly through replication of their genetic material, can take control of various intracellular signaling cascades, such as NF-κB, PI3K / Akt, MAPK signaling pathways or the protein

Ubiquitination System (UPS). Collected evidence suggests that curcumin is involved in antiviral activity by modulating many cell signaling pathways [15].

Zandi K, et al. [16] also demonstrated the inhibitory effect of curcumin on the development of several types of viruses [17]. Curcumin can directly inhibit the expression of early viral replication genes, e.g. HSV-1 [18], as well as inhibit the activity of HIV-1 integrase, which is necessary for replication of this virus [19].

In addition to integrase, the development of Human Immunodeficiency Virus (HIV) also requires other viral enzymes such as reverse transcriptase, protease, as well as Tat, a trans-activator of transcription. Curcumin has been shown to inhibit not only HIV integrase but also protease through direct intermolecular bonds with HIV protease and integrase active centers [20]. Curcumin activity is enhanced by the coordination binding of the keto-enol group of two curcumin with the boron atom in the HIV-1 and HIV-2 protease [21]. Among many plant therapeutics with electrophilic properties, curcumin inhibited 55% of Tat-dependent HIV transcription [22] (Figure 3).

Ginger

Chilli peppers

Turmeric

Unfortunately, accounts for only 2-5% of curcumin, and it also has poor oral absorption. Its bioavailability is low due to low absorption from the intestine. The bioavailability of curcumin significantly increases presence of capsaicin - a well-known natural substance rich in chili peppers [23]. Hot peppers, producing to capsaicin, have a stimulating effect on the immune system. It turns out that dendritic cells – a key antigen-presenting cells involved in the formation of an immune response have a receptor for this compound! These cells present the antigen to T lymphocytes as a response to infection, and capsaicin intensifies this process. Researchers have proven capsaicin effect, among others against HSV-1, HSV-2, IAV or MNV.

Lawrence RS, et al. [24] in their research suggest that nerve fibers sensitive to capsaicin play a role in the pathogenesis of primary and recurrent HSV infections. Capsaicin appears to reduce the severity of cutaneous HSV infections by interfering with the spread of the virus.

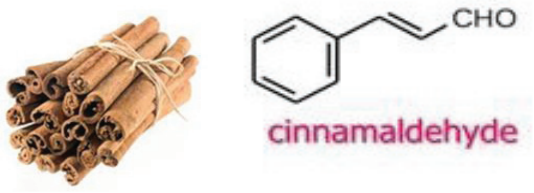
Tang K, et al. [25] in the study built a library of 40 natural products from dietary supplements and evaluated their anti-LASV effects. This study first revealed the effect of capsaicin as an LASV entry inhibitor and thus as a direct antiviral substance. These researchers have shown that capsaicin inhibits LASV entry by blocking the viral fusion through affecting the stable signal peptide transmembrane region of the LASV surface glycoprotein. As a dominant capsaicinoid, capsaicin is known as an agonist of the vanilloid receptor type 1 (TRPV1) or capsaicin [26] receptor, causing " hot "and burning sensation associated with chili pepper as a spice. This bioactivity has found clinical use as an analgesic in the treatment of peripheral neuropathic pain associated with HIV and herpes zoster [27-29].

However for ginger, the action of controlling viruses such as IAV influenza virus, herpes (HSV-2), RSV (Respiratory Syncytial Virus), rhinovirus, retrovirus or calicivirus (FCV), which is a surrogate of the human norovirus. The main active compounds in ginger are 6-szagaol and gingerol. Gingerol also reduces the formation of RTF (Reactive Oxygen Species, ROS) in human keratinocytes [30].Test results of aqueous clove and ginger extracts have been shown that they may prevent Food-borne viral infection (FCV). The antiviral test was performed using dilutions of the extracts below maximum non-toxic concentrations. Dose-dependent inactivation of FCV was observed when the host cells were treated with clove and ginger extract during or after infection at concentrations equal to or lower than the maximum non-toxic concentrations. The main bioactive compounds identified were eugenol and propanodiol [31]. Both clove extract and one of the main compounds in their essential oil (eugenol) have shown anti-viral activity, against influenza (H7N3) or herpes (HSV-1). Similar effects were shown by cinnamaldehyde present not only in Ceylon cinnamon (against HCV) or anethole in anise (against HSV-1),

as well as many other compounds and aromatic oils [32]. Eugenol may damage viral envelopes in freshly formed virons, which may cause inhibition of viral replication at an early stage [33]. The anti-viral activity of eugenol, carnation flower bud extract and essential oil against the Herpes simplex virus has been studied [33]. Direct inactivation of viruses and inhibition of intracellular and extracellular viruses has been observed. In the study of antiviral activity against HSV-1 and HSV-2, a 50% reduction in virus activity was found at 25.6 µg/ml and 16.2 µg / ml for HSV-1 and HSV-2, respectively. Eugenol has shown a synergistic effect with acyclovir against herpetic replication *in vitro* [32].

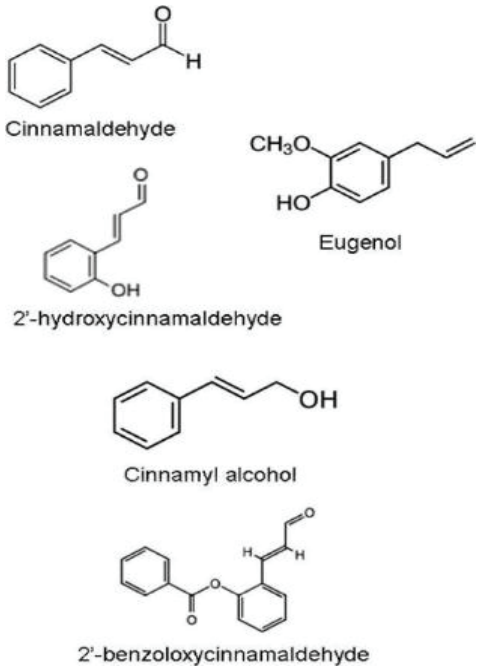
Cinnamon

Cinnamon contains many biologically active compounds. These compounds are responsible for the anoxidative, antibacterial, anti-inflammatory properties of cinnamon. Cinnamon bark contains many substances: tannin, resin, sugars, and a large amount of oily substances and essential oils. Among the latter, the most important is cinnamaldehyde, which constitutes about 70-80% of all cinnamon bark extract oils, 2% is eugenol, about 20% proanthocyanin and about 3% catechin [34] (Figure 4).



Munazza F, et al. [35] studied cinnamon bark extract and its nanoparticles for H7N3 influenza A virus in Vero cells, and cell viability was determined by the tetrazole dye (MTT) test. Nanoparticles derived from cinnamon extract enhanced antiviral activity and proved effective after incubation prior to virus infection. To determine the safety profile, cinnamon and its corresponding nanoparticles were tested for their cytotoxic activity at Verocells. Extract and nanoparticle concentrations (up to 500 µg/ml) were found to be non-toxic to Vero cells. Biosynthesized nanoparticles can therefore be a promising approach for treatment against influenza viral infections.

Ovadia M, et al. [36] studied the effect of CE (Cinnamon Extract) on HIV-1 activity on MT2 cells (CD4 + T cells) using a syncytia formation model in cell culture. 0.5 mg/ml of CE, was incubated with 50 µl of virus for 5 minutes in a final volume of 200 ul of RPMI medium at room temperature. After 3 days of incubation at 37 ˚C in a humidified 5% CO2 incubator, it was observed that 8-10 µg CE in 8-10 was sufficient to completely neutralize the virus (Figure 5).



Cinnamon extract compounds

Flowers of cloves

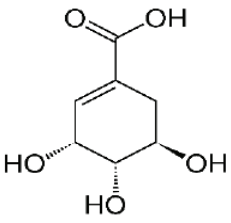
Wu S, et al. [37] studied a blend of wild orange, clove, cinnamon, eucalyptus and rosemary oils. In terms the mechanism of inhibiting viral infectivity via oil was also investigated [38]. Efficacy against H1N1 influenza virus has been demonstrated. These results are consistent with previous work, which showed that EO (Essential Oils) had antiviral activity

on H1N1 and HSV1 [39] directly inactivating free virus particles by disrupting virion envelope structures required for entry into host cells [39,40]. Commonly used antiviral drugs (eg acyclovir and ganciclovir) inhibit DNA polymerases [41].

Anise

A anise, produces shikimic acid, which is of great pro-health importance. Shikimic acid accounts for about 7% of the weight of the spice. Shikimic acid is one of the main active ingredients of drugs for flu treatment. Morover, anise contains essential oils, rich in many different antioxidant substances. Significant ingredients anise essetial oil (80%) are trans-anethol, cis-anethole, etragol, anisealdehyde. Anise is credited with numerous pro-health properties, mainly antiviral, antifungal and antibacterial [42] (Figure 6).

Anise



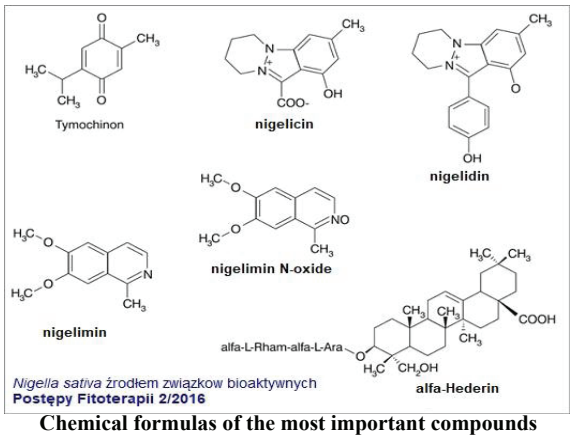
Shikimic acid

Cumin (Cuminum cyminum) seeds have longbeen used as antiseptic and disinfectant in India. Cuminaldehyde, cymene, and terpenoids are the major bioactive constituents of cumin Esential Oils (EOs). Hamed A. El-Serehy experiment aims to assess the antiretroviral effect of Cuminum cyminum seed extract [43]. In addition, the cytotoxicity and antioxidant properties of this plant extract were performed using the DPPH test. The total phenol content in C. cyminum seeds was shown to be 22.08 µg / mg dried extract, while the flavonoid concentration was 15.81 µg / mg dried extract. Morover, alcohol extract from cumin seeds at 4 µg / ml in 61% inhibits the development of herpes simplex viridae HSV-1 and 49% HSV-2. In addition, the results indicated that 137.4 µg / ml of the extract showed a 50% reduction in free radical activity (DPPH test) [44].

The cumin biologically active compound 1-(2-ethyl, 6-heptyl) phenol (EHP), may be responsible for these and other properties. EHP is active against many pathogens, as well as anti-tumor activity against six types of cancer cell lines (HEPG2, HELA , HCT116, MCF7, HEP2, CACO2) [45].

Black Cumin

Black cumin (*Nigella sativa L.*) - plant species of the family Ranunculaceae, having antioxidant properties associated with the reduction of free radicals such as DPPH (stronger for black seeds than for vitamin C) and nitric oxide, activity against nonenzymatic lipid peroxidation in microsomes. In their reaserch, Kawther ZS, et al. [46] postulate the effects of Black Cumin seed extracts on viral diseases, cancer, and angiogenetic disorders and oxidative stress. *N. sativa* was found to act against HIV and also against HCV in a numer of independent studies [47,48]. In the others study, NS exhibited immune-stimulant effects as depicted by enhanced cell-mediated, humoral immune responses and cytokine gene expression leading to early viral clearance, reduced pathogenicity of H9N2 possibly by inhibiting replication of viruses [49] (Figure 7).



Chemical formulas of the most important compounds

Nigella sativa L.

Contained in black cumin seeds

Yimer EM, et al. [50] found that *N. sativa* seed oil reduces viral load in a murine model Cytomegalovirus (CMV) infection to undetectable levels in the liver and spleen after 10 days of intraperitoneal administration of the extract [50]. This was probably due to an

increase in the number and function of CD4 + T cells and increased production of Interferon (INF-) gamma.

Patients with Hepatitis C Virus (HCV) who were not eligible for IFN-α/ribavirin treatment showed a significant improvement in HCV titer (16.67% became seronegative and 50% showed a significant decrease) after 6 months treatment of black cumin seeds oil [51-54].

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