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REVIEWS

ANTI-INFLAMMATORY PROPERTIES OF PLANT-DERIVED ORGANOSULFUR COMPOUNDS: INSIGHTS FROM SULFORAPHANE AND ALLICIN

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ABSTRACT

INTRODUCTION: In recent decades, there has been an increasing interest in the potential of bioactive compounds in food to reduce the risk of inflammation-related pathological disorders. Organosulfur compounds are known to benefit human health due to their anti-inflammatory effects.

AIM: This mini-review focused on the latest published scientific evidence about the anti-inflammatory effects of sulforaphane from broccoli and allicin from garlic.

MATERIALS AND METHODS: A screening of the latest scientific publications in specialized databases was done using specific keywords.

RESULTS: An overview of the effects of each compound in cell cultures, animal models, and human interventional studies on inflammation is provided. The molecular mechanisms behind anti-inflammatory effects are also commented on. The promising positive outcomes from many in vivo and in vitro studies are a basis for human dietary interventional studies.

CONCLUSION: Both compounds exert strong anti-inflammatory effects but, unlike sulforaphane, allicin seems to have more limitations in human interventions due to some undesirable effects.

Keywords: *organosulfur compounds, sulforaphane, allicin, pro-inflammatory markers, anti-inflammatory potential*

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INTRODUCTION

Inflammation is a complex process emerging in the body as a response to noxious stimuli such as viral, bacterial, or fungal infection and tissue damage. Although it is fundamentally a mechanism to protect the body from pathogens, repair injured tissues, and restore altered homeostasis, inflammation also has a pathological profile (1). The pro-inflammatory factors that activate and mediate inflammatory signals

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are associated with the aetiology of many pathological conditions, including neurodegenerative and cardiovascular diseases, diabetes, obesity, cancer, pulmonary, and autoimmune disorders.

Due to the enormous number of studies devoted to understanding the mechanisms of inflammation at the cellular and molecular level, numerous factors were identified as playing a role in this process, such as transcription factors, cytokines and chemokines, enzymes, adhesion molecules, receptors, etc. These components of inflammatory pathways are the main targets in the treatment of diseases with inflammation-related pathogenesis (2,3).

Scientific data accumulated in recent decades revealed the potential of active compounds in foods, mainly of plant origin, to suppress inflammatory response by inhibiting many pro-inflammatory markers (4). It has been found that organosulfur compounds, sulforaphane from cruciferous vegetables and allicin from garlic, have the potential to prevent various pathological processes, including chronic inflammation through the mechanism of inhibition of nuclear transcription factor kappa B (NF-kB), and hence the expression of its target genes: interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNFα), inducible nitric oxide synthase (iNOS), and inducible cyclooxygenase (COX-2) (5,6,7). Furthermore, sulforaphane and allicin have been shown to exert cytoprotective effects by activating the nuclear erythroid factor (Nrf2) signalling pathway, leading to increased levels of key antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR), thus preventing the cell oxidative stress (8,9,10).

Sulforaphane is the common name for 1-isothiocyanato-4-methylsulfinylbutane (11), a member of the organosulfur compounds found in plants of the *Brassicaceae* family with highest concentrations in broccoli sprouts. (12). The highly reactive sulforaphane is synthesized in plants from the inert precursor glucoraphanin (13). After mechanical disruption of the plant integrity, glucoraphanin is converted to sulforaphane by the action of the enzyme myrosinase (β- thioglucosidase, EC 3.2.1.147). Myrosinase is present both in plant tissue and in the human intestinal microbiota (14,15).

The biological activities of sulforaphane have been widely studied, revealing a range of health benefits, such as anti-inflammatory, anticancer, antioxidant and neuroprotective properties (16,17,18,19). The anticarcinogenic action of this isothiocyanate is associated with its potential to modulate the activity of phase II enzymes of xenobiotic metabolism. In addition, sulforaphane is reported to have antidiabetic properties revealed by its potential to improve insulin resistance and glucose tolerance (20).

Allicin (3-prop-2-enylsulfinylsulfanylprop-1-ene) according to the National Center for Biotechnology Information (11), is the main organosulfur compound released from crushed garlic after conversion of its precursor alliin. This process includes two steps – first, alliin is converted to allylsulfenic acid and dehydroalanine by the enzyme alliinase and in the second step, spontaneous condensation of two molecules of allylsulfenic acid forms allicin (21). Allicin is the compound in the *Allium* genus that gives the specific pungent flavour and aroma of the plants (22). The beneficial biological activities of garlic as food are attributed to allicin. The antimicrobial and antifungal properties of allicin are empirically proven. This natural antibiotic is reported to inhibit many species of microorganisms, including some highly pathogenic bacteria such as *Mycobacterium tuberculosis*, *Escherichia coli*, *Klebsiella proteus*, *Streptococcus* spp., *Staphylococcus* spp., *Helicobacter pylori* (21,23). Furthermore, allicin is reported to exert a range of other beneficial biological activities. Its anti-inflammatory, anticancer, and antioxidant properties are demonstrated in a variety of scientific studies (24).

In this mini-review, we focus on the potential of two of the most active organosulfur compounds, sulforaphane and allicin, to beneficially affect various markers of inflammation demonstrated in a variety of studies. The authors believe that the review will expand knowledge about the potential of sulforaphane and allicin as natural sources of new dietary supplements and therapeutics with anti-inflammatory effects.

AIM

The aim of the present review was to compare sulforaphane and allicin regarding their anti-inflam-

matory effects explored in various *in vitro* and *in vivo* models and interventional studies.

MATERIALS AND METHODS

The present review was done by screening the latest scientific publications in databases, such as PubMed, ScienceDirect, Google Scholar, and ResearchGate using combinations of the following keywords: "sulforaphane", "allicin", "pro-inflammatory markers", "organosulfur compounds", "anti-inflammatory potential". Most of the papers included in the review were published in the last five years.

RESULTS AND DISCUSSION

Evidence from in vitro studies

The anti-inflammatory potential of sulforaphane and allicin was demonstrated in *in vitro* models of inflammation by various types of cell cultures. Several studies demonstrated the potential of sulforaphane to reduce the mRNA levels of TNF-α, IL-1β, IL-6, and the COX-2 and iNOS at transcriptional or protein levels in LPS-stimulated macrophages and human umbilical vein endothelial cells (HUVEC) (25). Zhang and Wu (2021) (26) estimated in their study the potential of sulforaphane to mitigate LPS-induced injury of Caco-2 cells. It is worth mentioning the established opposite effect of sulforaphane depending on the presence or absence of a pro-inflammatory stimulus. In a model of TNF-α stimulated synoviocytes, sulforaphane selectively induced apoptosis in inflammation-stimulated cells and at the same time increased the vitality of unstimulated control cells (27). Most of the studies suggested that the probable mechanism by which sulforaphane mediates its anti-inflammatory effects is the inhibition of NF-kB expression or blocking its nuclear translocation (28,29,30).

Similarly, allicin was reported to manifest anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and enzymes in certain *in vitro* models (24,25,31). It was reported that administration of garlic extract significantly attenuated the production of pro-inflammatory mediators, such as nitric oxide, prostaglandins, TNF-α, and IL-6 in LPS-stimulated RAW 264.7 macrophages in a dose-dependent manner. Authors suggested that allicin could exert this effect through the inhibition of mitogen-activated protein kinases (MAPK) and NF-κB signalling pathways (32). In a cell culture of cardiomyocytes, allicin was shown to alleviate LPS-induced injury by suppressing the production of inflammatory mediators and increasing cell viability and survival (33). In addition, several studies reported that allicin can induce apoptosis of inflammation-injured cells, revealing its therapeutic potential against cancer and other pathological conditions related to low-grade systemic inflammation (24,34,35). Furthermore, this compound was demonstrated to ameliorate the mitochondrial dysfunction in LPS-associated injury in HUVEC (36).

Several comprehensive reviews summarized data about the anti-inflammatory effects of sulforaphane and allicin from *in vitro* models in various types of cells (24,25,37). Based on the reported data, there is no doubt that these organosulfur compounds have pronounced anti-inflammatory properties with the potential to modulate pro-inflammatory mediators and thus to beneficially affect pathological conditions with different aetiology. Moreover, due to the overlapping of their anti-inflammatory effects, these compounds probably share common mechanisms of action since they can affect the same signalling pathways, modulating transcriptional factors and enzymes such as NF-κB, MAPK, Nrf2, COX-2, and iNOS in different research studies (16,24,27)

Evidence from in vivo studies

In addition to *in vitro* evaluations, many *in vivo* studies were carried out to explore the anti-inflammatory effects of sulforaphane and allicin. Although most of the models of inflammation-related conditions differ in methods to induce inflammation and in the routes of sulforaphane and allicin administration, the results are promising in terms of the potential of the two compounds to be used as therapeutics or adjuvants in different pathological conditions.

In a mice model of neuropathic pain, the intraperitoneal administration of sulforaphane dose-dependently attenuated pain hypersensitivity by reduction of pro-inflammatory cytokine levels and COX2 and iNOS, and by upregulation of the anti-inflammatory IL-10. In addition, the same study reported that the increased levels of μ-opioid receptors, usually observed in sciatic nerve injury, were enhanced due to the sulforaphane treatment (38). In a model of induced colitis, the treatment of mice with brocco-

li seed extract resulted in a reduction in pathogenic flora, increased activity of antioxidant markers, increased levels of the anti-inflammatory interleukin IL-10 and decreased levels of the pro-inflammatory interleukins IL-1β, IL-6, and TNF-α (39). In addition to these data, sulforaphane exhibits anti-inflammatory effects in models of LPS-induced acute lung injury, muscle inflammation, hypoxic pulmonary hypertension, and type 2 diabetes mellitus (T2DM) (25,40,41).

Results in support of the anti-inflammatory properties of allicin were also reported in various animal models. For example, allicin exerts significant hepatoprotective effects by reducing hepatocyte apoptosis and inflammation in carbon tetrachloride-induced liver injury in mice. The authors reported that these effects were comparable to the effects of glycyrrhizin – a compound from liquorice roots with proven hepatoprotective effects (42). Furthermore, it was reported that 30 days of allicin treatment of Wister rats with metabolic syndrome significantly reduced overexpression of IL-1β, IL-6, and TNF-α in plasma and renal cortex (43). The beneficial effects of allicin on the central neuron system (CNS) were also demonstrated by *in vivo* models. Intraperitoneal administration of the compound alleviated experimentally induced intracerebral haemorrhage in mice by various pharmacological effects, including upregulation of pro-inflammatory factors such as IL-6 and C-X-C motif ligand 2 in the brain (44).

Furthermore, several studies explored the neuroprotective potential of allicin. It was observed that allicin significantly prevented and ameliorated ischaemic stroke by modulating markers of oxidative stress and inflammatory response (45). In addition, allicin was shown to ameliorate aluminium- and copper-induced cognitive dysfunction in rats by restoring the redox balance and reducing the inflammatory cytokines in the brain (46).

Evidence from human interventional studies

Several epidemiological studies have indicated that the consumption of vegetables, rich in bioactive phytochemicals, including organosulfur compounds is associated with a lower occurrence of inflammation-related chronic disorders, such as cardiovascular diseases, obesity, cancer, neurological disorders, etc. (47,48,49,50).

The beneficial findings from *in vitro* and *in vivo* studies could not be extrapolated directly for human beings. The human intervention studies have some limitations in proving the results from experimental animal and cell culture studies. The main reason could be the poor bioavailability of the studied substances in plasma and tissues, toxicity, and possible undesirable side effects. For example, it has been found that polyphenols are utilized in insignificant amounts in the human body and have low bioavailability due to the action of intestinal microbiota and also due to their metabolism in the liver as xenobiotics (51). This raises the question of to what extent the beneficial effects of natural biologically active substances can be expected to be reproduced in human interventions.

Sulforaphane was shown to have high bioavailability (around 80%) compared to some polyphenols usually included in dietary supplements (47) and to be relatively safe at low doses in human trials (52). However, further research is needed on the toxicity and side effects of high doses of sulforaphane when the goal is to achieve higher bioavailability and better therapeutic effects.

Reports from two randomized double-blind intervention studies revealed that sulforaphane levels increased significantly in circulation following the consumption of broccoli (53) and significantly accumulated in certain tissues after a 28-day intervention with capsules containing its precursor glucoraphanin (54). A review of human intervention studies with sulforaphane, primarily through broccoli sprout consumption, indicated improvements in oxidative stress markers and some evidence of reduced inflammation, though the results were less consistent compared to animal studies (55). Furthermore, broccoli sprout consumption for 70 days significantly decreased IL-6 levels and CRP in the plasma of obese subjects (56). In a recent randomized, double-blind, placebo-controlled, cross-over designed study with a cohort of young athletes, 30 mg sulforaphane daily prevented muscle inflammation by reducing the IL-6 levels 24 hours after intensive exercise (57). In addition, the potential of sulforaphane as a supplement or as an adjuvant to anti-inflammatory therapies is being intensively investigated. Several clinical trials with broccoli sprout extracts (two in Europe and

five in the USA) published in the National Library of Medicine platform were recently completed (58).

Regarding allicin, due to its volatility and rapid metabolism, its bioavailability is relatively low, even when consuming large amounts of chopped raw garlic (59). It was shown that products of allicin metabolism, such as S-allyl cysteine and S-all mercapto cysteine, are more stable, easily absorbed in the gastrointestinal tract and available in the liver, kidney, and plasma after one hour of the intake (25). Most human studies have focused on the effects of garlic extract containing allicin rather than pure allicin. However, it is important to pay attention to some specific features of allicin metabolism. Entering the circulation and cells, allicin is rapidly bound via disulfide bonds to cysteine residues of glutathione and proteins to form S-allyl-mercapto products. Because of this tendency to oxidize thiol groups, allicin can be considered a reactive sulfur species (60). This may be a limitation in predicting the amount of garlic that needs to be eaten to reach the therapeutically relevant bioavailability of allicin contained in it. Moreover, allicin was reported to stimulate pain-sensitive neurons and thus interventions with a high amount of this compound could be harmful. In addition, many side effects of fresh garlic consumption were reported, such as gastrointestinal disturbances, nausea, bad breath, and body odour (61).

Despite these limitations, several randomized controlled trials demonstrated that supplementation with garlic or aged garlic extract in tablets or capsules formulation significantly reduced the level of circulating C-reactive protein (CRP) and TNF-α (62) Supplementation with aged garlic extract was shown to

Table 1. Summary of beneficial effects of sulforaphane and allicin demonstrated in different type of studies.

Type of Studies	Sulforaphane	Allicin
***In vitro* studies**	Anti-inflammatory effect through inhibition of NF-kB (28, 29, 30) Decrease TNF-α, IL-6, COX-2, iNOS in LPS-stimulated HUVEC (25) Mitigates LPS-induces injury of Caco-2 (26) Has a potential to induce apoptosis in TNF-α-stimulated synoviocytes (27)	Pro-inflammatory cytokines and enzyme inhibition (24, 25, 31, 37) Dose-dependent inhibition of MAPK and NF-kB signalling pathways in LPS-stimulated RAW 264.7 macrophages (32) Alleviates LPS-induced injury and increases the viability of cardiomyocytes (33) Therapeutic potential against cancer and low-grade inflammation (24, 34, 35) Ameliorates the mitochondrial dysfunction in LPS-induced injury in HUVEC cells (36) Tends to oxidize thiol groups (60)
***In vivo* studies**	Attenuated pain by reduction of COX-2, iNOS, and upregulation of IL-10, and increase of the levels of μ-opioid receptors in a mice model of neuropathic pain (38) Reduced pathogenic flora and increased antioxidant markers in a model of induced colitis in mice (39) Anti-inflammatory effects in T2DM and lung-injured animal models (40, 41)	Hepatoprotective effect by reducing hepatocyte apoptosis and inflammation in induced liver injury in mice (42) Decreases IL-1ß, IL-6, TNF-α in plasma and renal cortex in metabolic syndrome rats (43) Neuroprotective effect (44, 45, 46)
Human interventional studies	Broccoli sprout consumption improves oxidative stress and inflammation biomarkers (55) 70 days of broccoli sprout supplementation decreases IL-6 and CRP in obese subjects (56) Sulforaphane, in a dose of 30 mg/daily, decreases IL-6 and prevents muscle inflammation in young athletes (57)	Stimulates pain-sensitive neurons, gastrointestinal disturbance, nausea, bad breath (61) Garlic or its extracts decrease CRP and TNF-α (62) Aged garlic extract inhibits systematic inflammation through a decrease in TNF-α, IL-6, and IL-8 in overweight subjects (63)

reduce circulating levels of TNF-α, IL-6, IL-8, and thus to inhibit the systemic inflammation in overweight subjects (63).

Together, these clinical trials and epidemiological studies provided valuable evidence supporting the anti-inflammatory and health-promoting effects of organosulfur compounds, particularly sulforaphane and allicin.

The beneficial effects of sulforaphane and allicin in *in vitro*, *in vivo,* and human interventional studies are summarized in Table 1.

CONCLUSION

Both sulforaphane and allicin exhibit significant anti-inflammatory properties, demonstrated in animal models and cell culture studies. Although limited, human interventional studies also suggest potential benefits in reducing inflammation and oxidative stress in various inflammation-related pathological conditions.

The anti-inflammatory effects of sulforaphane and allicin often overlap probably due to their potential to affect the same signalling pathways. Both compounds reduce inflammatory cytokine production by modulating NF-kB and Nrf2 signalling pathways but, unlike sulforaphane, allicin generates numerous side effects.

It could be suggested that sulforaphane and allicin are promising agents to be included in anti-inflammatory therapies, targeting the signalling pathways that generate pro-inflammatory cytokines, chemokines, and enzymes. However, more extensive and well-designed clinical trials are needed to confirm these effects and fully understand their therapeutic potential in humans.

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