

Review

The Potential Application of *Allium* Extracts in the Treatment of Gastrointestinal Cancers

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Abstract: Herbal medicine is currently widely practiced, since natural resources are reported to alleviate side effects during oncological treatment while modifying cancer cell responses at the same time. *Allium* vegetables and their constituents have recently been extensively investigated due to the numerous possible beneficial properties, establishing them as an additional treatment modality in different cancers. According to the epidemiological evidence, as well as many in vivo and in vitro studies, the abovementioned substances seem to be effective in the prevention and inhibition of the progression of carcinogenesis. Due to high concentrations of organosulfur compounds, which exhibit anticarcinogenic, antimicrobial, as well as anti-inflammatory properties, *Allium* constituents are believed to constitute a promising prevention and supportive therapy for oncological patients. Besides, it was demonstrated that a combination of *Allium* extracts with chemotherapy provided satisfactory clinical outcomes while at the same time being cost-effective. The aim of this review was to present and discuss currently investigated *Allium* extracts and their effects on several gastrointestinal cancers including gastric, colon, liver, esophageal, and pancreatic cancer.

Keywords: *Allium*; *Allium* extract; garlic; gastrointestinal cancers; gastric cancer; esophageal cancer; liver cancer; pancreatic cancer; colorectal cancer; colon cancer



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1. Introduction

The usage of medical herbs dates back to ancient times when they were used to relieve both physical and mental pain, while they are still widely applied and continually investigated nowadays due to their numerous advantages in various fields of medicine. *Allium* vegetables constitute a group of flowering plants belonging to the Amaryllidaceae family, which are currently one of the most prevalently used in medicine [1]. The Amaryllidaceae family consists of more than 850 different species, among which garlic (*Allium sativum*), onion (*Allium cepa*), leeks (*Allium tuberosum*), chives (*Allium schoenoprasum*), and shallot (*Allium hirtifolium*) are most often used for medical purposes [2]. Recently, there has been increasing interest in the application of allium vegetables—*Allium sativum* (*A. sativum*) or *Allium cepa* (*A. cepa*) in particular—as well as their constituents and extracts as a potential therapeutic strategy in a vast number of cancers including gastric cancer, colon cancer, liver cancer, pancreatic cancer, esophageal cancer, breast cancer, lung cancer, or prostate cancer [3–5]. Except for potential anticarcinogenic properties, *Allium* vegetables and their constituents have been shown to modulate immune functions by activating macrophages and inducing T-cell proliferation, provide radioprotection, modulate reactive oxygen species (ROS) formation, and might possibly have antiaging properties because of their antioxidant activities [6–10]. During the processing of *Allium* vegetables, a significant number of flavonoids, saponins, and organosulfur compounds (OSCs) is produced, presenting the ability to inhibit cellular proliferation as well as to induce the cell cycle arrest or

apoptosis of cancer cells, along with other cancer chemopreventive effects [11]. Numerous in vitro studies showed a high cytotoxic activity of the active compounds (OSCs, flavonoids, saponins) found in *Allium* vegetables, which currently allows for further investigations regarding the development of new anticancer drugs. However, the presence of particular active compounds is also associated with the form in which the vegetable is served—for instance, crushed garlic contains significant amounts of different OSCs, while when it is cooked, it mostly contains only diallyl disulfide (DADS) and diallyl trisulfide (DATS) (Figures 1 and 2) [12].

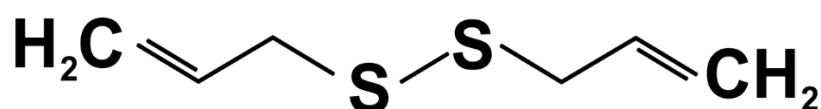


Figure 1. The chemical formula of diallyl disulfide.

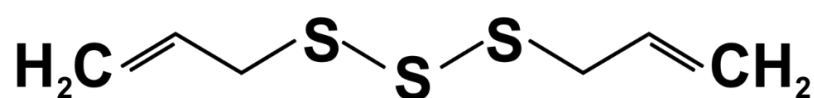


Figure 2. The chemical formula of diallyl trisulfide.

Except for OSCs, both of the abovementioned garlic derivatives—DADS and DATS—present anticancer properties (inhibition of mutagenesis and cellular proliferation, induction of apoptosis and cell cycle arrest, prevention of oxidative stress and damage) and are investigated as possible chemopreventive agents. Additional anticancer effects of the abovementioned substances encompass the control of the activation of carcinogenic intermediates and enzymes (modulation of cancer metabolism), histone modification, inhibition of DNA adducts formation, and inhibition of angiogenesis; however, it must be considered that the intensity of those effects depends on the type of treated cancer along with the dose of a particular substance [13–15]. Other *Allium* derivatives include diallyl sulfide (DAS), diallyl tetrasulfide, allicin, S-allyl, S-allylcysteine (SAC), or S-allylmercaptocysteine (SAMC) (Figure 3) [16,17]. It was demonstrated that SAC and SAMC enabled the restoration of E-cadherin in studies on human cell lines, and thus it was proposed that these substances might be beneficial in the reversal of the epithelial-mesenchymal transition (EMT) during carcinogenesis [18–21].

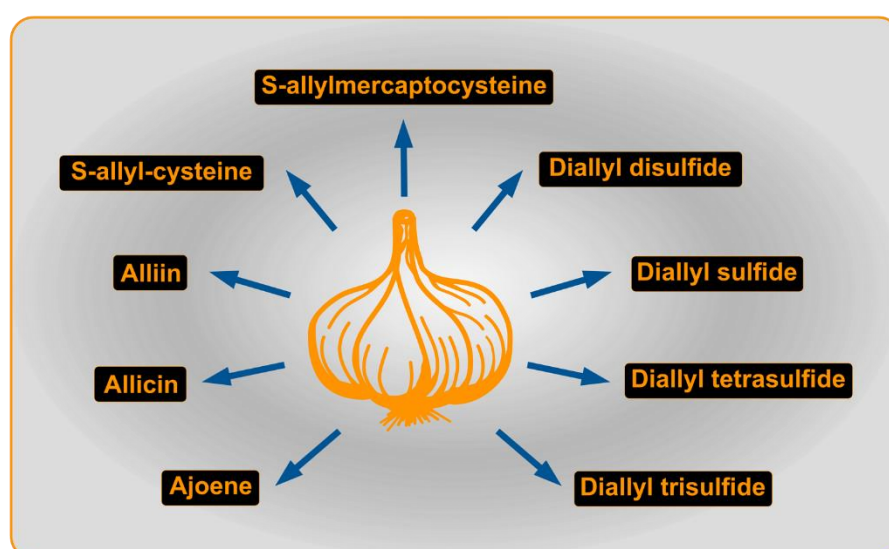


Figure 3. Active constituents derived from garlic.

Due to the numerous abovementioned properties (anti-inflammatory, antioxidant, antimicrobial, anticancer), *Allium* vegetables and their extracts were shown to have many

potential health benefits, and their utility in the prevention and treatment of a wide range of disorders and impairments is still investigated. Except for constituting a potentially effective therapeutic strategy for gastrointestinal malignancies, *Allium* and its constituents showed beneficial effects in terms of several cardiovascular and renal diseases; they also exert hepatoprotective, antiobesity, antidiabetic, and neuroprotective activities [22].

The aim of the following review is to present the most updated knowledge about the application of *Allium* vegetables and their constituents as a possible optional treatment of gastrointestinal cancers. We performed a literature search on PubMed, Cochrane, and EMBASE databases on 15 February 2021. The total number of articles (relevant to the topic of this review) included in the final analysis was 67 with a time range of 1996–2020. To the best of the authors' knowledge, it is the most recently updated review that summarizes findings regarding the potential application of *Allium* and its constituents in the prevention and treatment of gastrointestinal cancers specifically. Thus, another objective of this review is to provide an insight into what is currently investigated, while at the same time indicating the potential aspects that could be further evaluated by researchers improving the management of gastrointestinal carcinogenesis.

2. Gastric Cancer

Gastric cancer constitutes one of the most prevalent malignancies worldwide, and since it is the fourth leading cause of cancer-related deaths, there is an urgent need to seek the most effective treatment strategies either as early prevention (primarily as a protection against *Helicobacter pylori* (*H. pylori*) infection) or as therapy for early or advanced stages of gastric carcinogenesis [23–26]. Quite recently, there has been increasing interest in the possible application of *Allium* and its constituents as an additional treatment option for patients with gastric cancer as a part of the implementation of herbal medicine in the field of oncology. Some research pointed out strong evidence for the consumption of *Allium* vegetables and the reduced risk of gastric cancer and precancerous gastric lesions [27–30]. It was reported that the consumption of garlic (or its supplements), onions, or leeks significantly reduced the risk of any digestive disorders including gastric cancer compared to the groups with the minimum intake of the abovementioned vegetables [31]. A recent study by Li et al. showed that seven-year garlic supplementation was significantly associated with either a reduced risk of gastric cancer or a reduced risk of cancer-related death [32]. This was primarily associated with the presence of high amounts of OSCs in *Allium* vegetables, which showed their anticancer effects in both in vivo and in vitro studies.

One of the constituents derived from *Allium chinense*—(25R)-5 α -spirostan-3 β -yl-3-O-acetyl-O- β -D-glucopyranosyl-(1 \rightarrow 2)-O-[β -D-glucopyranosyl-(1 \rightarrow 3)]-O- β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-galactopyranoside (A-24)—presents an ability to inhibit the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, inducing apoptosis and autophagy of gastric cancer cells (SGC-7901 and AGS cell lines) [33]. Similarly, *Allium ursinum* extract (ramson) induces apoptosis and cell cycle arrest (in G₂/M phase) in the AGS gastric cancer cell line [34]. An organic sulfur compound—allicin—from the bulbs of *Allium sativum* induces apoptosis of gastric cancer cells by activating the p38 (mitogen-activated protein kinase pathway) MAPK signaling pathway, which further stimulates the hydroxylation of caspase-3 [35]. An animal model showed that high doses of DATS inhibited cellular proliferation, induced cell cycle arrest and apoptosis (by activating the MAPK and PI3K/AKT signaling pathways), suppressed tumor growth, significantly increased the TNF- α , IL-1 β , and IFN- γ levels, and induced the expression of E-cadherin while lowering MMP9 levels, at the same time contributing to the inhibition of EMT [36]. Similarly, DADS shows an ability to inhibit the growth and migration of cancer cells, mainly due to increased TIMP metalloproteinase inhibitor 1 and 2 (TIMP-1 and -2) levels and modulations within the tight junctions by downregulating claudin expression [37]. Another advantage of garlic supplementation is the blockage of oxidative damage by the upregulation of reduced-glutathione (GSH)-dependent hepatic detoxification systems in experimental models [38]. *Allium* constituents also tend to induce the upregulation of

cadherin-1 (CDH1) and cyclooxygenase 2 (COX-2) downregulation, further supporting the role of the *Allium* genus in gastric cancer chemoprevention [39]. *Allium*-derived flavonols, by inhibiting the PI3K/Akt signaling pathway, induce the apoptosis of gastric cancer cells in a caspase-dependent and mitochondria-mediated manner [40]. Besides, flavonoids that are highly present in *Allium* vegetables act as the triggers of the antioxidant systems [41]. Interestingly, garlic supplementation might protect the gastric mucosa against damages associated with alcohol consumption, which also constitutes another risk factor for gastric carcinogenesis [42]. What should be considered is that anticancer properties and the further reduced risk of gastric cancer present are observed mainly in a dose-dependent manner in most of the current studies [43]. As described above, *Allium* and its constituents present an ability to suppress gastric carcinogenesis by several mechanisms including the induction of apoptosis, autophagy, and cell cycle arrest of gastric cancer cells, while at the same time decreasing the rate of their proliferation. What also seems to be clinically relevant is that these substances are reported to have an effect on the EMT by altering the levels of E-cadherin and claudins. This is consequently associated with the lowering of the migration properties of cancer cells and hence a decrease in the metastatic potential.

Except for the anticancer properties, *Allium* vegetables are widely known for their antibacterial properties, which—in terms of gastric cancer—are crucial, as one of the most prevalent causes of this malignancy is *H. pylori* infection. For instance, allicin present in ethanolic garlic extract or acetonetic garlic extract inhibits the growth of *H. pylori* in in vitro studies [44]. Therefore, *Allium* constituents might play a protective role by preventing excessive *H. pylori* growth and ultimately lowering the risk of gastric cancer, which seems to be a satisfactory method for the early prevention of carcinogenesis [45]. Even though some research has provided satisfactory results in this matter, the available data remains contradictory and requires further evaluation for definite conclusions [46,47].

3. Colon Cancer

Chemoprevention of colon cancer is of great importance since it is one of the major causes of cancer-related deaths nowadays. Similar to gastric cancer, different *Allium* constituents were shown to modify the risk of colon cancer and reduce the mortality rates associated with this malignancy [48–51]. Supplementation of garlic or its extracts reduces the number of aberrant crypt foci, which are one of the earliest preneoplastic lesions of colon cancer, and leads to the inhibition of COX-2 transcriptional activity [52–54]. Likewise, the consumption of *Allium* vegetables is also associated with a reduced risk of colorectal adenomatous polyps [55]. The prevention of precursor lesions' (adenomatous polyps, crypt foci) formation seems to be an effective strategy to provide an early prevention of colon carcinogenesis. OSCs derived from garlic have been shown to induce cytotoxicity, cell cycle arrest with apoptosis, as well as an enhanced ROS production in colon cancer cell lines. DAS, DADS, and DATS were shown to inhibit the viability and motility of colon cancer cells by inhibiting MMP-2, MMP-7, and MMP-9 [56]. Besides, the abovementioned compounds present an ability to inhibit COX-2, PI3K, and nitric oxide synthase (iNOS), leading to the inhibition of cellular proliferation. The intake of foods—such as *Allium* vegetables—rich in flavonoids is significantly associated with a reduced risk of colon cancer [57]. *Allium* constituents also affect apoptotic pathways, which was shown by increasing the apoptotic index associated with programmed cell death [58]. One of the pathomechanisms related to the induction of apoptosis by garlic extracts includes an enhanced ROS production, whereas the antiproliferative effects are attributed to the downregulation of extracellular signal-regulated kinase 2 (ERK-2), cyclin B1, and cdk1 expression [59,60]. Further, apoptosis might be stimulated by an enhanced caspase-3 activity in a mitochondrial-dependent manner, as was demonstrated in the case of the application of a crude extract of garlic [61].

Interestingly, allicin combined with X-ray radiotherapy inhibits the proliferation and migration of colon cancer cells, while at the same time inducing their apoptosis; the mechanism of the enhanced sensitivity of X-ray radiotherapy might be associated with

the inhibition of the NF- κ B signaling pathway by allicin [62]. The involvement of the NF- κ B pathway is also observed in the case of the inhibition of colon cancer cells' proliferation during thiocresonone (garlic-derived sulfur compound) application [63]. *Allium* extracts also show a potential to inhibit angiogenesis, significantly suppressing tumor growth by inhibiting the tube formation of the endothelial cells [64]. One of the OSCs present in garlic—alliin/s-allyl cysteine sulfoxide (SACS)—has been proposed as one of the potential drugs for colorectal cancer treatment [65]. Moreover, it was proposed that a combination of *Allium* extracts with 5-fluorouracil (5-FU) or oxaliplatin might be an effective treatment strategy for colon cancer patients [66]. The abovementioned strategy also seems to be promising due to the lower doses of chemotherapeutics needed to achieve similar clinical outcomes compared to chemotherapy alone. Therefore, according to the recent studies, *Allium* and its constituents could act as an additional treatment option, enhancing other therapeutic strategies and consequently leading to potentially more favorable outcomes for patients.

4. Liver Cancer

Liver cancer constitutes the sixth most prevalently diagnosed cancer worldwide [67]. Since the overall clinical outcome along with the 5-year survival rate are still unsatisfactory, there is a need to upgrade the available treatment strategies to seek new treatment modalities. Epidemiological evidence presents that a diet rich in *Allium* vegetables is significantly associated with a reduced risk of liver cancer [68]. Data shows that the consumption of raw garlic twice or more per week might be a protective factor against liver cancer [69]. Besides, garlic intake might also alleviate the side effects of various therapeutic-induced liver injuries [70]. DAS, DADS, and DATS are effective in inducing apoptosis and inhibiting the cellular proliferation of hepatic cancer cells at the same time [71,72]. DATS, by controlling the expression of Cdk7 and B1, might lead to the arrest of cancer cells in the G2/M phase, inhibiting cellular proliferation [73]. A synergistic effect was achieved during a concomitant treatment with garlic extracts and silymarin with that combination suppressing the formation of N-nitrosodiethylamine (NDEA) responsible for the induction of ROS formation and hepatotoxicity [74]. *Allium atrovioleaceum* shows antiproliferative properties exerted on the human hepatocarcinoma cells as well as proapoptotic effects by downregulating Bcl-2 expression and by the subsequent overactivation of caspase-3 [75]. A synergistic effect was achieved by combining *Allium atrovioleaceum* with doxorubicin. Extracts of *Allium atrovioleaceum* show an ability to induce apoptosis in a p53-dependent manner; the anticancer effects were shown to be dose-dependent [76]. Likewise, allicin regulates proapoptotic and autophagic cell death pathways dependent on p53 [77]. SAC was also shown to inhibit the proliferation, invasion, and angiogenesis of hepatic cancer cells, and a synergistic effect was observed while combining it with cisplatin [78]. SAC is involved in the modulation of E-cadherin, which affects EMT and thus the potential migration and invasion of hepatic cancer cells. It was demonstrated that hexane extracts of garlic gloves were effective in inducing the apoptosis of hepatic cancer cells as well as the intracellular formation of ROS with different subsequent mitochondrial dysfunctions [79]. Aged garlic extracts suppress the putative paraneoplastic lesions, confirming their chemopreventive effects [77]. It was suggested that water garlic extracts might be more effective than DADS in the treatment of liver cancer; however, this thesis must be evaluated through further research [80]. High amounts of flavonoids are associated with reduced hepatotoxicity and liver protection [81]. As has been so far presented, those substances seem to also be effective when combined with other treatment strategies. The early prevention of carcinogenesis, alleviation of drug-induced side effects, and modulation of tumor microenvironment properties are the most rational arguments that support the administration of *Allium* and its extracts to liver cancer patients as well as to those who are at higher risk of its development.

5. Esophageal Cancer

Esophageal cancer is characterized by its aggressive nature along with poor clinical outcome and survival rate in patients. Since treatment modalities such as surgery do not always provide satisfactory results, agents that might relieve its symptoms or act as preventive factors are continually sought after. The intake of *Allium* vegetables such as garlic or onion was reported to show protective effects against the induction of squamous cell carcinoma of the esophagus [82–85]. Increased garlic intake is inversely associated with the risk of esophageal cancer in the general population with an emphasis on individuals who overuse tobacco or alcohol [86]. OSCs seem to act as a protective factor, decreasing the risk of esophageal cancer [87]. Disulfide in ajoene (a rearrangement product of allicin) induces G₂/M cell cycle arrest and apoptosis by overactivation of caspase-3, inhibiting the growth of esophageal cancer cells [88]. Even though the consumption of *Allium* vegetables seems to be effective in the prevention of esophageal cancer, the literature is still scarce, and this aspect should be investigated in further studies. These substances might potentially act as an early prevention of esophageal cancer; nevertheless, very little is known about the effects exerted by these substances in in vitro studies on esophageal cancer cells specifically, which might be considered for further research.

6. Pancreatic Cancer

Pancreatic cancer is one of the most quickly devastating and fatal cancers, whose prevention and proper treatment remain unsatisfactory yet. Similar to other gastrointestinal cancers, the increased intake of fresh fruit and vegetables (*Allium* in particular) is associated with a lower risk of preneoplastic lesions and the onset of pancreatic carcinogenesis [89]. For instance, garlic oil reduces the survival rate of pancreatic cancer cells, inhibits cellular proliferation, and promotes apoptosis in a concentration-dependent manner [90]. Likewise, allicin suppresses viability, DNA damage with epigenetic alterations, caspase-dependent apoptosis, and cell cycle arrest of pancreatic cancer cells along with an accompanying ROS generation [91]. Apoptotic signaling pathways are also triggered by Fas, cyclin B1, cyclin D, Bcl-2, and Akt, which was demonstrated by using DATS on pancreatic cancer cell lines; besides, cyclin D1 was observed to induce the overexpression of p53, additionally increasing DATS toxicity on cancer cells [92]. Another *Allium* constituent—DADS—shows an ability to inhibit the H₂S/CSE-SP/NK1R-NF-κB signaling pathway, inhibiting the progression of acute pancreatitis, which is considered a risk factor for pancreatic cancer (Table 1) [93].

Similarly to other gastrointestinal malignancies described in this review, *Allium* extracts might potentially constitute an additional or complementary treatment strategy, enabling a possible reduction of costs while providing an early prevention and effective inhibition of carcinogenic mechanisms.

Table 1. Molecular effects exerted by *Allium* and its constituents on cancer cells.

Malignancy	Mechanism	Result
Gastric Cancer	↓ PI3K/Akt/mTOR pathway	↑ apoptosis, autophagy
	↑ p38 MAPK pathway → caspase-3 hydroxylation	↑ apoptosis
	↑ MAPK and PI3K/Akt pathways	↓ cellular proliferation ↑ cell cycle arrest ↑ apoptosis
	↑ TIMP-1 and TIMP-2 → ↓ claudin	↓ growth and migration
	↑ GSH-dependent hepatic detoxification systems	↓ oxidative damage
	↑ CDH1 and ↓ COX-2	enhanced chemoprevention
Colon Cancer	↓ MMP-2, MMP-7, MMP-9	↓ viability and motility
	↓ COX-2, PI3K, iNOS ↓ ERK-2, cyclin B1, cdk1	↓ cellular proliferation
	↑ ROS ↑ caspase-3 ↓ NF-κB pathway	↑ apoptosis
Liver Cancer	↓ NDEA	↓ ROS
	↓ Bcl-2 → ↑ caspase-3	↓ cellular proliferation ↑ apoptosis
Esophageal Cancer	↑ caspase-3	↑ apoptosis ↑ G ₂ /M cell cycle arrest
Pancreatic Cancer	↓ H ₂ S/CSE-SP/NK1R-NF-κB	suppression of acute pancreatitis

7. Conclusions

Currently, due to the significant increase in morbidity and mortality rates because of carcinogenesis, there is an urgent need to seek safer and more effective therapeutic agents to improve the clinical outcome of oncological patients. *Allium* vegetables and their constituents have recently been deeply investigated in many cancers including those within the gastrointestinal tract that were discussed in this review. The abovementioned substances seem to be an additional modality constituting both a protection and optional treatment strategy (alone or combined with chemotherapy) in many cancers due to their wide spectrum of beneficial properties. *Allium* and its constituents present anti-inflammatory, immunomodulatory, as well as anticancer effects that were observed in many in vivo and in vitro experiments, and these are mainly exerted due to the presence of high concentrations of OSCs. *Allium* constituents and extracts might be taken in many different forms, and the currently available data seem to confirm their utility for the prevention of many disorders and cancers of the gastrointestinal tract. Moreover, these substances could potentially act as an early prevention of gastrointestinal malignancies, which could possibly reduce the morbidity and mortality risk to some extent, while at the same time being more cost-effective; however, more research and evaluations are required in this matter.

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Abbreviations

5-FU	5-fluorouracil
CDH1	Cadherin-1
COX-2	Cyclooxygenase 2
DADS	Diallyl disulfide
DAS	Diallyl sulfide
DATS	Diallyl trisulfide
EMT	Epithelial-mesenchymal transition
ERK-2	Extracellular signal-regulated kinase 2
GSH	reduced glutathione
<i>H. pylori</i>	<i>Helicobacter pylori</i>
iNOS	reduced glutathione
MAPK	Mitogen-activated protein kinase
NDEA	N-nitrosodiethylamine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OSCs	Organosulfur compounds
PI3K/Akt/mTOR pathway	Phosphatidylinositol-3-kinase/protein kase B/mamma
ROS	Reactive oxygen species
SAC	S-allylcysteine
SACS	S-allyl cysteine sulfoxide
SAMCTIMP-1 and -2	S-allylmercaptocysteineTIMP metalloproteinase inhibitor 1 and 2

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