

EDIBLE *ALLIUM* SPECIES: CHEMICAL COMPOSITION, BIOLOGICAL ACTIVITY AND HEALTH EFFECTS

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ABSTRACT

Since ancient times edible *Alliums* play an important role in human diet and traditional medicine. The most commonly cultivated *Allium* species are onion (*Allium cepa* L.), garlic (*Allium sativum* L.), leek (*Allium ampeloprasum* L.), chive (*Allium schoenoprasum* L.) and Welsh or Japanese bunching onion (*Allium fistulosum* L.). These species are rich sources of biologically active compounds such as flavonoids, organosulfur compounds and saponins. Numerous studies we reviewed in this paper, confirmed their significant antioxidant, antibacterial, anti-inflammatory, antiproliferative and anticancer activities, which makes them an important source of phytonutrients that can contribute to the protection and preservation of human health.

Keywords: *Alliums*, biological activity, flavonoids, organosulfur compounds

1. INTRODUCTION

Allium species have been used for centuries in human diet because of their pungent smell and specific taste, but also for medicinal purposes because of their remarkable medicinal properties. The best known and most cultivated species of the genus *Allium*, onion (*Allium cepa* L.) and garlic (*Allium sativum* L.) are widely used as spices and medicinal plants and are therefore the subject of numerous studies. To date, their chemical structure has been thoroughly explored as well as their biological activity. *Allium* species are rich in phytonutrients, mostly flavonoids and organosulfur compounds which exhibit strong antioxidative, antimicrobial, anti-inflammatory and anticarcinogenic activity (AHLIABOR *et al.*, 2016; ALBISHI *et al.*, 2013; ASHRAF *et al.*, 2011; BENEKEBLIA, 2004; BOROWSKA *et al.*, 2013; CHANG *et al.*, 2013; COLINA-COCA *et al.*, 2017; HERMAN-ANTOSIEWICZ and SINGH, 2004; JOHNSON *et al.*, 2016; KAUR *et al.*, 2016; KHAZAEI *et al.*, 2017; KIM *et al.*, 2013; KOCA *et al.*, 2016; KUMARI and RANJAN, 2014; KWON *et al.*, 2002; LANZOTTI *et al.*, 2014; LANZOTTI, 2006; LI *et al.*, 2016; LI *et al.*, 2014; MIN KIM *et al.*, 1997; NDOYE FOE *et al.*, 2016; ORTIZ, 2015; PAN *et al.*, 2018; QUINTERO-FABIÁN *et al.*, 2013; SHIN *et al.*, 2013; SULEIMAN and ABDALLAH, 2014; THOMAS *et al.*, 2017; THOMSON and ALLI, 2003; YANG *et al.*, 2001b).

Many epidemiological studies showed that regular consumption of *Allium* vegetables can decrease the risk of various diseases such as cardiovascular, respiratory, gastrointestinal diseases and different types of cancer (CHEN *et al.*, 2009; FLEISCHAUER *et al.*, 2000; GONZÁLEZ *et al.*, 2006; GUERCIO *et al.*, 2014; KIM *et al.*, 2018; O'GARA *et al.*, 2000; POURZAND *et al.*, 2016; TURATI *et al.*, 2015, 2014; YOU *et al.*, 1989; ZHOU *et al.*, 2011).

2. CHEMICAL COMPOSITION

The chemical composition of these species is very complex. They contain a variety of different phytochemicals, and the most important constituents are organosulfur compounds. These compounds provide them with characteristic odor and flavor, as well as the majority of biological properties. Another important group of chemically active compounds are polyphenols, which include phenolic acids and flavonoids, responsible for the characteristic color of onion bulbs. Edible onion parts are rich in carbohydrates, mostly glucose and fructose, while the outer scales of onion bulbs contain significant content of galactose and arabinose. Essential amino acids (arginine and glutamic acid), which may be important nitrogen reserves, also contribute to the nutritional value of onion species. They also contain several other complex bioactive components such as saponins, vitamins (A, C, B6, and folate) and minerals (P, K, Ca, Mg, Zn, Mn, Na, Fe, Br, J, Se, and Cu).

2.1. Flavonoids

Flavonoids are the largest group of polyphenolic compounds present in fruit, vegetables, nuts, tea, wine and other food ingredients. Common onion (*A. cepa* L.), garlic (*A. sativum* L.), and other *Allium* species are the richest sources of dietary flavonoids.

The best described property of flavonoids is their antioxidant activity. Their structure is essential for their ability to act. The configuration, substitution and number of hydroxyl groups determine their antioxidant activity and ability to scavenge free reactive species. Flavonoids have a characteristic structure with two benzene rings (A and B rings, shown in Fig. 1) connected with a pyran ring (heterocyclic ring containing oxygen, the C ring, shown in Fig. 1).

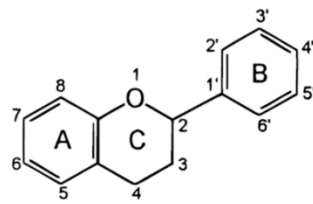


Figure 1. The basic structure of flavonoids (PIETTA, 2000).

So far, more than 4000 different kind of flavonoids have been identified. They are divided into groups (Fig. 2) by the number and position of hydroxyl groups, level of oxidation and pattern of substitution of the C ring: i) anthocyanins - glycosylated derivative of anthocyanidin, present in colorful flowers and fruits; ii) anthoxanthins - a group of colorless compounds divided in several categories, including flavones, flavonols, flavanones, flavanols, isoflavones and their glycosides (HAN *et al.*, 2007). Two flavonoid classes are mainly found in onion, flavonols, responsible for yellow and brown skin and anthocyanins which give red to purple color to some onion varieties (RODRIGUES *et al.*, 2017).

Flavonoid	Basic structure
Flavones	
Flavonols	
Flavanones	
Flavanols	
Anthocyanidins	
Isoflavones	

Figure 2. Chemical structure of the main classes of flavonoids (REIS GIADA, 2013).

Flavonoids are plant pigments, which participate in plant protection against different ecological and physiological stresses such as UV radiation, heat, herbivores and pathogens. Flavonoids have been shown to possess a diverse biological property such as antioxidant, anti-inflammatory, antiallergic, antimicrobial, antiviral, anticancer and neuroprotective activity. These properties are structure dependent which makes flavonoids one of the best antioxidants, scavengers of free radicals and a chelator of bivalent cations that cause DNA damage which is associated with the development of many diseases (HALLIWELL *et al.*, 2005; PANCHE *et al.*, 2016).

Anthocyanins and flavonols are the most common subgroups of flavonoids present in *Allium* species. The most abundant flavonols in common onions are two quercetin conjugates, namely quercetin 3,4'-diglucoside and quercetin 4'-monoglucoside (CARIDI *et al.*, 2007; FREDOTOVIĆ *et al.*, 2017; GRIFFITHS *et al.*, 2002). These compounds together account for about 80% of total flavonol content with some differences among various *Allium* cultivars.

Quercetin, myricetin, kaempferol and isorhamnetin glycosides accounted for the remaining 15% total of flavonols in onions. Compared to yellow and white onions, red onions showed higher total flavonol content (PRAKASH *et al.*, 2007). Also, total flavonol content is higher in the outer layers compared to the inner layers of onion bulb.

In addition to flavonoids, onions are rich source of anthocyanins. Anthocyanins are class of natural pigments responsible for the color of fruits, vegetables, flowers and grains. They give red or purple color to outer layers of onion bulbs. The most frequent anthocyanins in red onion are cyanidin derivatives (over 50% of all anthocyanins), cyanidin-3-(6"-malonylglucoside), cyanidin-3-(6"-malonyl-3"glucosyl-glucoside) and cyanidin-3-glucoside. There are also minor amounts of peonidin, petunidin and delphinidin derivatives (FERRERES and GIL, 1996; FOSSEN *et al.*, 1996; GENNARO *et al.*, 2002; RODRIGUES *et al.*, 2017; SLIMESTAD *et al.*, 2007).

2.2. Organosulfur compounds

Allium species are characterized by the rich content of sulfur compounds such as S-alk(en)yl cysteine sulfoxide (ACSO), sulfides, alkyl polysulfides and amino acids (WHO, 1999). First sulfur compounds were isolated from *Allium* species in the middle of the 19th century (SEMMLER, 1892; WERTHEIM, 1844). It has been discovered that volatile sulfur compounds are responsible for the pungent odor of onion species. Also, it became clear that these disulfide compounds are not present in intact bulbs, but they are formed by the enzymatic cleavage of precursors upon disruption of the bulb tissue. Alliin or (+)-S-allyl-cysteine sulfoxide, was the first odorless sulfur compound isolated from the cytoplasm of intact garlic cell (STOLL and SEEBECK, 1948).

After crushing the onion cell, the enzyme allinase is released from vacuole. The enzyme allinase belongs to the group of C-S lyases and plays a key role in the formation of volatile compounds of the genus *Allium* (KEUSGEN, 2011). ACSO is decomposed by the enzymatic reaction of allinase to pyruvate, ammonia and sulfenic acid. Sulfenic acid immediately produce thiosulfinates by a quick condensation reaction (BLOCK *et al.*, 1992). Thiosulfinates are very unstable and break down to the mixture of compounds, responsible for specific onion taste: polysulfides, thiosulfinates, capaenes and zwiebelanes (Fig. 3). The main thiosulfinate in garlic is diallyl sulfide, derived from alliin, and dipropyl disulfide in common onion, derived from isoalliin (ROSE *et al.*, 2005). NDOYE FOE *et al.* (2016) identified the main components of *A. sativum* and *A. cepa* essential oil. *A. sativum* essential oil was rich in diallyl trisulfide, diallyl disulfide, allyl methyl trisulfide, diallyl sulfide and diallyl tetrasulfide while those from *A. cepa* was rich in diallyl trisulfide, dipropyl trisulfide, 2-methyl-3,4-dithiaheptane, methyl propyl trisulfide, dipropyl

tetrasulfide and 2-propenyl propyl disulfide. These compounds are most likely responsible for their excellent antioxidant and anti-inflammatory activity.

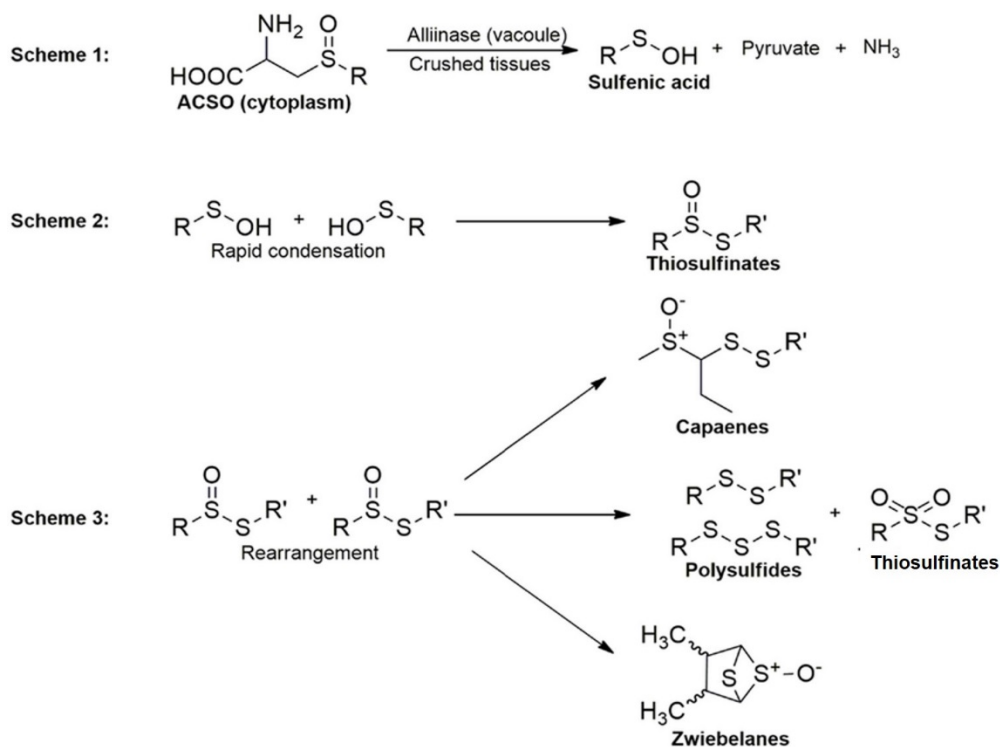


Figure 3. Overview of organosulfide formation from S-alk(en)yl-L-cysteine sulfoxide (ACS0) in *Allium* species (TOCMO *et al.*, 2015).

2.3. Other bioactive compounds

Recent scientific research found several interesting novel compounds isolated from onion such as saponins and peptides. They have been identified so far in over 40 different *Allium* species (SOBOLEWSKA *et al.*, 2016). Saponins are one of the largest classes of surface-active secondary metabolites widely distributed in plants, however, their biological functions are not completely understood. They are generally considered to have important roles in defense of plants against pathogens, pests and herbivores and several studies indicated that they can act as natural remedies in treatment of many diseases (AUGUSTI, 1990; LANZOTTI, 2006; MORRISSEY and OSBOURN, 1999; OSBOURN *et al.*, 2011; SOBOLEWSKA *et al.*, 2016; SPARG *et al.*, 2004). Recent study reported that saponins from *Allium* species possess high cytotoxic activity, which makes them potential candidates for future development as anticancer agents (LANZZOTI *et al.*, 2014).

3. BIOLOGICAL ACTIVITY AND HEALTH EFFECTS OF EDIBLE ONIONS

Onions are used since ancient times as vegetable and spice because of their special taste and smell. They were also used in folk medicine for treatment of bacterial infections such as dysentery, ulcers, wounds, scars, keloids, and asthma. They have also been used as an

adjuvant therapy for diabetes, for prevention of high blood pressure, and loss of appetite (WHO, 1999).

Over the last 50 years, an intensive research has been conducted on the evaluation of biological activity of *Allium* plants, their extracts and essential oil. Garlic and onion are the best known and two mostly tested *Allium* species. Garlic extracts have been reported to possess strong antibacterial (BENEKEBLIA, 2004), antidiabetic (ASHRAF *et al.*, 2011), antiproliferative activity (THOMSON and ALI, 2003; YANG *et al.*, 2001a), and ability to inhibit development of cardiovascular diseases (THOMSON *et al.*, 2006). Similar but weaker effects have been proved for onion extracts.

3.1. Antioxidant activity

Allium plants are one of the main food antioxidants. Antioxidants prevent cell and DNA damage by chelating free oxygen or nitrogen radicals (ROS or RNS), inhibiting their production, or activating antioxidative enzymes (superoxide dismutase 2- SOD2, catalase-CAT and glutathione peroxidase- GP_x). Analysis of the antioxidant activity of *Allium* species is also important because of the proven link between oxidative stress and development of diseases such as atherosclerosis, various forms of cancer and even aging itself. The first study of antioxidant properties of *Allium* plants was performed with crude extracts. Investigators have concluded that the organosulfur compounds are primarily responsible for observed antioxidant effects (AUGUSTI, 1990; MIN KIM *et al.*, 1997; SIEGERS *et al.*, 1999a). YIN and CHENG (1998), and BENEKEBLIA (2004) concluded that antioxidant activity of onions is not just related with organosulfur compounds but also with phenolic compounds.

In vitro and *in vivo* data reported that onion extracts showed stronger ability to scavenge free radicals, compared to garlic extracts and red onion was more active than yellow onion (GORINSTEIN *et al.*, 2008; NUUTILA *et al.*, 2003). Red onion is the rich source of flavonoids especially quercetin, presented in conjugated form. The dry outer layers of onion, which are wasted during food preparation, contain huge amounts of quercetin and its derivatives (CORZO-MARTINEZ and CORZO, 2007). KAUR *et al.* (2016) proved that methanolic extract of *Allium cepa* have higher antioxidant activity compared to aqueous extract. Interestingly, it was observed that aqueous extract had higher phenolic content. KIM *et al.* (2005) investigated antioxidant activity of flavonols isolated from garlic leaves and shoots. They confirmed that quercetin and its compounds possess strong antioxidant activity. KUMARI and RANJAN (2014) study showed that methanolic extract of *Allium sativum* exhibited strong antioxidant activity, which is in correlation with rich phenolic content. FREDOTOVIĆ *et al.* (2017) determined antioxidant potential of two onion methanolic extracts, *Allium × cornutum* and *A. cepa*. Both onions showed strong antioxidant activity. However, *A. × cornutum* extract showed slightly higher antioxidant activity which was in correlation with his higher total phenolic content. Comparison of antioxidant activity of garlic and onion cultivars grown in Turkey showed that both species possesses good antioxidant properties which are significantly correlated with their total phenolic content (TPC). Among all samples of onion and garlic, red onions had the highest TPC and antioxidant activity (KOCA *et al.*, 2016). KIM *et al.* (2018) performed a comparative study of bioactive organosulfur compounds and antioxidant activity in three *Allium* species, *A. cepa* (onion), *A. sativum* (garlic) and *A. ampeloprasum* (elephant garlic). Results showed that garlic possessed the strongest antioxidant activity followed by elephant garlic and onion. Their findings demonstrated a positive correlation between antioxidant activity and organosulfur compounds content. The study of COLINA-COCA *et al.* (2017) confirmed that feeding rats with high-cholesterol (HC) diet resulted in oxidative stress. HC diet enriched with onion ingredients significantly decreased oxidative

stress by activating antioxidant defense system. BOYLE *et al.* (2000) performed an *in vivo* experiment and confirmed the powerful antioxidant effect of onions. They showed that consumption of food rich in flavonoids (in this experiment it was fried red onion) is associated with an increased resistance of human lymphocyte DNA to DNA strand breakage.

Different *Allium* species, both cultivated (*A. nutans* L., *A. fistulosum* L., *A. vineale* L., *A. pskemense* B. Fedtsch, *A. schoenoprasum* L., *A. cepa* L. and *A. sativum* L.) and wild (*A. flavum* L., *A. sphaerocephalum* L., *A. atrovioleaceum* Boiss, *A. vineale* L., *A. ursinum* L., *A. scorodoprasum* L., *A. roseum* L. and *A. subhirsutum* L.), were investigated in order to evaluate the antioxidant properties of their bulbs (ŠTAJNER *et al.*, 2008). The results confirmed that the bulbs and leaves of cultivated *Allium* species possess better antioxidant ability in comparison with other wild species, which makes them promising sources of non-toxic natural antioxidants. Therefore, the bulbs and leaves of *Allium* species could be used not only in human diet but also as a source of natural antioxidants and for medical purposes.

3.2. Antimicrobial activity

In 1858, Louis Pasteur described the antibacterial effect of garlic for the first time. During World War II garlic was used as an antiseptic to prevent gangrene (PETROVSKA and CEKOVSKA, 2010). Recent studies confirmed antibacterial properties of garlic. Garlic is effective against gram-positive and gram-negative bacteria, although its extracts were more effective on gram-negative bacteria (DANKERT *et al.*, 1979; ELNIMA *et al.*, 1983; YOSHIDA *et al.*, 1999a, 1999b). JOHNSON *et al.* (2016) showed significant antimicrobial potency of aqueous garlic extract against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Aqueous extracts of *Allium sativum* and *Allium tuberosum* were tested against penicillin-sensitive *S. aureus* (PSSA) and MRSA. Both extracts were able to reduce staphylococcal infection, although only *A. sativum* showed *in vitro* anti-staphylococcal activity, but neither of them wasn't effective against MRSA (VENÂNCIO *et al.*, 2017). HAN *et al.* (1995) showed that biological activity of 1 mg allicin works the same as 15 IU of penicillin. This proved that allicin and other organosulfur compounds present in garlic essential oil are responsible for strong antibacterial activity (ANKRI and MIRELMAN, 1999; MATSUURA, 1997). WALLOCK-RICHARDS *et al.* (2014) reported the first evidence for antimicrobial activity of allicin containing garlic extract against BCC (*Burkholderia cepacia* Complex), the major bacterial phytopathogen for alliums and intrinsically multiresistant human pathogen.

Red onion is not so effective against bacteria compared to garlic (BAKHT *et al.*, 2013; BENEKEBLIA, 2004; HUGHES and LAWSON, 1991; MIN KIM *et al.*, 1997; SANTAS *et al.*, 2010). Onion essential oil showed strong inhibitory effect on growth of gram-positive bacteria. Their water extracts showed strong *in vitro* inhibitory effect on growth of *Escherichia coli*, *Serratia marcescens*, *Streptococcus* sp., *Lactobacillus odontolyticus*, *Pseudomonas aeruginosa*, *Salmonella typhosa* and *Prevotella intermedia* (BAKRI and DOUGLAS, 2005). Raw onion extract showed good antimicrobial activity against *S. aureus* while boiled extract had no activity. In addition, the boiled onion extract showed no antimicrobial activity against both *S. aureus* and *E. coli* (ORTIZ, 2015). AHIABOR *et al.* (2016) confirmed antimicrobial activity of undiluted crude extracts of red and yellow onion (*A. cepa* L.) and shallot (*A. aescalonicum* L.) against *S. typhi*, *E. coli* and *S. aureus*. It is interesting that onion and garlic extracts can prevent growth and development of oral bacteria that cause caries (JAIN *et al.*, 2015; KIM, 1997; MISHRA *et al.*, 2016; THOMAS *et al.*, 2017).

Beside antibacterial effect, onion and garlic are also effective against broad spectrum of fungi and yeasts. Garlic showed strong inhibitory effect against *Candida* sp., *Cryptococcus*

sp., *Trichophyton* sp., *Epidermophyton* sp. and *Microsporum* sp. (ANKRI and MIRELMAN, 1999; DAVIS *et al.*, 1994; SHAMS-GHAHFAROKHI *et al.*, 2006; YAMADA and AZUMA, 1977) as well as against fungi that produce mycotoxins such as *Aspergillus parasiticus*, *A. niger*, *A. flavus* and *A. fumigates* (BENEKEBLIA, 2004; YIN and TSAO, 1999). Recent research showed antifungal effect of garlic essential oil against three *Trichophyton* species (*Trichophyton rubrum*, *T. erinacei*, *T. soudanense*) responsible for severe mycoses in humans (PYUN and SHIN, 2006). Water extract of red onion was effective against *Malassezia furfur* and *Candida* sp. (SHAMS-GHAHFAROKHI *et al.*, 2006). The newest studies are consistent with those published research and confirm strong antifungal activity of garlic aqueous and petroleum ether extracts as well as garlic oil tested on *Candida albicans* (LI *et al.*, 2016), *Aspergillus*, *Curvularia* and some *Dermatophyte* species (SULEIMAN and ABDALLAH, 2014).

Allium species stimulate growth of probiotic bacteria (genus *Lactobacillus* and *Bifidobacterium*), which can ferment oligosaccharides, prebiotics that human organism cannot digest on its own. Ingestion of probiotic bacteria may reduce the severity and frequency of diarrheal diseases, and development of colon cancer as well as improve lactose digestibility among lactose-intolerant individuals (KAPLAN and HUTKINS, 2000). LI *et al.* (2016) investigated the effect of onion juice on milk fermentation by *Lactobacillus acidophilus*. The onion juice stimulated the growth of probiotic bacteria *L. acidophilus* and maintain their viability. The authors assume that whole constituents of onion juice including polyphenols, sulfur compounds, minerals and fructans together are responsible for stimulation of growth and viability of *L. acidophilus*.

3.3. Anti-inflammatory activity

It has been proved that most of the *Allium* members possesses anti-inflammatory effect. Mechanism of their anti-inflammatory action can be explained through the interaction of oxidative stress and inflammation. Overexpression of pro-inflammatory enzymes such as iNOS (inducible nitrogen oxide synthetase) and COX-II (cyclooxygenase) is noticed in some diseases such as atherosclerosis, some types of cancer and inflammatory diseases. Their overexpression leads to production of pro-inflammatory mediators such as NO (nitrogen oxide) and PG (prostaglandin) which play important role in maintenance of normal blood pressure, inflammatory processes, wound healing and regulation of body temperature (REUTER *et al.*, 2010).

However, their overexpression can also lead to development of diseases such as colon cancer, atherosclerosis, inflammatory bowel diseases, multiple sclerosis and Alzheimer disease. iNOS and COX-II enzymes which activate mediators are under control of transcriptional factor NF- κ B. NF- κ B controls the expression of more than 150 different genes included in regulation of inflammatory processes. Recent research has been proved that antioxidants can inhibit activation of NF- κ B, and thus reduce the symptoms, and development of mentioned diseases and conditions (DEVI *et al.*, 2009)

Quercetin and apigenin are potent inhibitors of nitric oxide (NO) and prostaglandin E2 (PGE2) production induced by lipopolysaccharide (LPS) in the macrophage cell line J774A.1 (RASO *et al.*, 2001). They modulate iNOS and COX-II enzyme expression. Reduced activity of both enzymes by the action of apigenin and quercetin affects the expression of NF- κ B (WADSWORTH and KOOP, 1999). Modulation of iNOS and COX-II enzymes by these two flavonoids may be important in the prevention of inflammation and indicate that they might be used as potent anti-inflammatory agents. Three active garlic compounds, caffeic acid, S-allyl cysteine and uracil inhibited UVB-induced skin wrinkle formation in mice by decreasing oxidative stress as follows: i) caffeic acid and S-allyl cysteine decrease oxidative stress by direct affecting and modulating NF- κ B or AP-1

(activator protein 1), ii) all three active compounds achieve anti-inflammatory effect through the suppression of COX-2 and iNOS (KIM *et al.*, 2013). SAC, caffeic acid, uracil, diallyl trisulfide, diallyl sulfide and other garlic compounds can inhibit activity of NF- κ B by inhibiting transcription of cytokine genes involved in proinflammatory response. Phenolic extract isolated from onion skin showed the potency of inhibition human LDL cholesterol oxidation and COX-2 expression even at concentrations as low as 5 μ g/ml (ALBISHI *et al.*, 2013). QUINTERO-FABIÁN *et al.* (2013) examined the effects of alliin in lipopolysaccharide- (LPS-) stimulated 3T3-L1 adipocytes by RT-PCR, Western blot, and microarrays analysis of 22,000 genes. The phosphorylation of ERK1/2, which is involved in LPS-induced inflammation in adipocytes, was decreased following alliin treatment. Also, the gene expression profile by microarrays showed an upregulation of genes involved in immune response and downregulation of genes related with cancer. Their results have shown that alliin is able to suppress the LPS inflammatory signals by generating anti-inflammatory gene expression profile and by modifying adipocyte metabolic profile.

Garlic prevents oxidation of low density lipoprotein (LDL). The oxidation of LDL is under control of lipoxygenase (LOX) and inducible NO synthase (iNOS) whose activity is regulated by transcriptional factor NF- κ B. Oxidized LDL promotes adhesion and platelet aggregation, which stimulates the inflammatory process, resulting in damage of cardiovascular system and development of diseases such as atherosclerosis. Garlic water extract and its main component, S-allyl cysteine (SAC) inhibits iNOS in human macrophages and thus reduce oxidation of LDL (GENG *et al.*, 1997; IDE and LAU, 2001). Thanks to its strong antioxidative capacity, SAC can remove superoxide radical that reacts with NO and thus prevent its activity. Diallyl-disulfide (DADS) also can decrease NO production, expression of proinflammatory cytokines and protein expression in RAW264.7 murine macrophage cell line (SHIN *et al.*, 2013) Garlic extract and its main compound SAC, may be useful for prevention of atherosclerosis (Kim *et al.*, 2001).

KIM *et al.* (2005) isolated four flavonols from garlic leaves and shoots and checked their antioxidant activity by measuring inhibition of lipoxygenase (LO) and hyaluronidase (HYA). Quercetin showed the strongest antioxidant activity while its glycosides, isoquercitrin and reynoutrin showed slightly lower activity. Allicin, the active substance of garlic, inhibited degradation of I κ B (inhibitor of transcriptional factor NF- κ B). The degradation of I κ B releases active NF- κ B, which is then translocated to the nucleus and regulates gene expression. Inhibition of NF- κ B reduce proinflammatory cytokine expression and synthesis of inflammatory enzymes COX/LOX (LANG *et al.*, 2004). ALI *et al.* (2000) demonstrate that *A. cepa* and its thiosulfates can inhibit COX and LOX activity, as well as platelet aggregation in the blood. They also confirmed antiasthmatic activity of onion extract and ability to inhibit cancer development. JAISWAL and RIZVI (2014) explored the effect of onion extract in the regulation of PON1 (paraoxonase 1) expression in male Wistar rats subjected to mercuric chloride induced oxidative stress. PON1 is an important enzyme with capability of protection against low-density lipoprotein (LDL) oxidation. Onion extract significantly decreased mercuric chloride induced oxidative damage by up-regulating the activity of PON1 enzyme and protected against LDL-oxidation and lipid peroxidation.

3.4. Antiproliferative and anticancer activity

Antiproliferative effect of *Allium* species have been reported in several studies using different cell cultures. SEKI *et al.* (2000) reported about the ability of garlic and onion oil to inhibit proliferation of human promyelocytic leukemia cells. Interesting experiment of SIEGERS *et al.* (1999b) showed that garlic powder and extract alone are unable to inhibit

tumor cell growth, but when extract and garlic powder are supplemented simultaneously, there was a significant inhibition of cell proliferation. They suggested that antiproliferative effect of garlic is due to the catalytic break-down of alliin induced by alliinase enzyme. After catalytic breakage of alliin, allicin and polysulfides are synthesized, which are responsible for such a powerful antiproliferative effect.

It was also found that onionin A, a natural compound isolated from onion, strongly inhibited ovarian cancer cell proliferation, so it could be used for additional treatment of patients with ovarian cancer (TSUBOKI *et al.*, 2016). FREDOTOVIĆ *et al.* (2017) demonstrated strong antiproliferative effect of methanolic extracts of two onion species, triploid onion *A. × cornutum* and *A. cepa*, on glioblastoma and breast cancer cell lines. The inhibition of glioblastoma cell growth was stronger than the inhibition of breast cancer lines in both onion extracts treatments.

As we have already mentioned, *Allium* species are rich sources of flavonoids and organosulfur compounds. The molecular mechanism of antiproliferative action is related with both type of compounds. Quercetin glucosides (Q 3,4'-diglucoside and Q 4'-monoglucoside), isolated from four *Allium* species, *A. chinese* (Chinese onion), *A. sativum* (garlic), *A. cepa* L. (onion) and *A. fistulosum* L. (Welsh onion) showed to be an effective inhibitor on cell growth of HepG2, PC-3 and HT-29 cells (PAN *et al.*, 2018). These results suggest that combination of quercetin glucosides may be responsible for antiproliferative activity of onion extracts on cancer cells (LI *et al.*, 2014). CHANG *et al.* (2013) demonstrated that among all isolated glucosides from onion extract, Q 4'-monoglucoside exhibited the highest antioxidant activity on cancer cells. They also suggested that quercetin glucosides may act as activators of apoptosis in different cancer cell lines. The antiproliferative action of flavonoids may involve the inhibition of the prooxidant process. Flavonoids are effective inhibitors of xanthine oxidase (CHANG *et al.*, 1993), COX and LOX (MUTOH *et al.*, 2000), and therefore they inhibit tumor cell proliferation. Also, they can inhibit polyamine biosynthesis. Ornithine decarboxylase is enzyme involved in polyamine biosynthesis and correlated with the rate of DNA synthesis and cell proliferation in different tissues. Different experiments showed that flavonoids are able to inhibit ornithine decarboxylase and decrease polyamine level leading to inhibition of DNA synthesis and cell proliferation (MAKITA *et al.*, 1996; TANAKA *et al.*, 1997a, 1997b). The antiproliferative effect of organosulfur compounds seems to be related with their ability to induce apoptosis. The study of SUNDARAM and MILNER (1996) showed that DADS (diallyl disulfide) can reduce the growth of colon, lung and skin tumor cells. DADS' antiproliferative activity depends on the presence of both diallyl and disulfide groups. The antiproliferative mechanism of DADS and DATS (diallyl trisulfide) is related with the increase of the intracellular free-calcium concentration which may activate calcium-dependent endonuclease leading to DNA fragmentation and apoptosis (SAKAMOTO *et al.*, 1997; SUNDARAM and MILNER, 1996). DATS possesses anticancer activity both *in vitro* and *in vivo*. BOROWSKA *et al.* (2013) showed that DATS is more toxic to prostate cancer cells than to noncancerous epithelial cell line PNT1A. Cytotoxicity of DATS toward PNT1A cell line was reduced which means that PNT1A cells had higher resistance to DATS-induced cell death than PC-3 cells. DADS also induced apoptosis in HL60, HCT-15 and neuroblastoma cells by the production of ROS followed by the induction of p53 and activation of caspase-3 which leads to cell death (FILOMENI *et al.*, 2003; HONG *et al.*, 2000; KWON *et al.*, 2002). DADS can also affect the cell cycle in human HCT-15 cells. It can induce G2/M phase arrest and inhibition of p³⁴ kinase activity because of the decreased p³⁴/cyclin B1 complex formation and subsequent p³⁴ hyperphosphorylation (KNOWLES and MILNER, 2000). YANG *et al.* (2009) demonstrated that DADS induced ROS formation and accumulation of Ca²⁺ ions, which induced the apoptosis by promoting caspase-3 activity in COLO 205 cells. Apoptosis is followed by the increased level of Fas,

phosphorylation of Ask1 and JNK, p53 and apoptotic genes Bak and Bax leading to the decrease of the antiapoptotic genes Bcl-2 and Bcl-X.

The flower extract of *A. atrovioleaceum* induced antiproliferative effect against the Hella cell line. The mechanism of its action seems to involve the induction of apoptosis through the down regulation of the antiapoptotic *Bcl-2* gene expression and activation of caspase-9 and caspase-3 mitochondrial death pathway (KHAZAEI *et al.*, 2017). SOUID *et al.* (2017) first demonstrated that dried aqueous extract (DAE) of *A. roseum* possesses an excellent antiproliferative effect on Chronic Myeloid Leukemia (CLM) K562 cells. The mechanism of DAE antiproliferative action was associated with the inhibition of both ERK_{1/2} and PI3K/Akt signaling antiapoptotic pathway and induction of apoptotic caspase pathway. Furthermore, DAE wasn't toxic for normal mouse fibroblast cells. Chemical analysis of DAE identified a different organosulfur compounds and high amount of allicin, which are known as potent anticancer agents.

Based on these findings, we can conclude that *Allium* vegetables possess exceptional antiproliferative activity against different cell lines (BOIVIN *et al.*, 2009). This activity is in correlation with their anticancer properties observed in many epidemiological and laboratory studies (FLEISCHAUER and ARAB, 2001; GALEONE *et al.*, 2006; MILNER, 2001; TALALAY and FAHEY, 2001). These effects are related with both flavonoid and organosulfur compounds.

Many epidemiological studies have shown that regular consumption of *Allium* vegetables is associated with decreased risk of developing cancer, especially gastrointestinal cancer (BIANCHINI and VAINIO, 2001; GAO *et al.*, 1999; LAWSON, 1998; WITTE *et al.*, 1996). Two cohort studies and meta-analysis of 19 case-control studies showed that consumption of high levels of *Allium* vegetables reduced risk for gastric cancer development (ZHOU *et al.*, 2011). The review with summarized findings from epidemiological studies based on *Allium* vegetables intake and gastric cancer risk once again confirmed the beneficial effect of this vegetables (GUERCIO *et al.*, 2014). They concluded that high intakes of alliums, mainly garlic and onion, can prevent gastric cancer development. New epidemiological studies are in line with those of GUERCIO *et al.* (2014). Results from case-control study and meta-analysis confirmed that high intake of alliums, garlic and onion, may reduce gastric cancer risk (TURATI *et al.*, 2015).

A large cohort study carried out in 10 European countries: the European Prospective Investigation into Cancer and Nutrition (EPIC) confirmed the link between increased intake of fruits and vegetables (including *Allium* vegetables) and decreased risk of stomach cancer development (GONZÁLEZ *et al.*, 2006). In a case-control study conducted in China, it was demonstrated that higher intake of red onion, garlic, Chinese onion, Welsh onion and leek was correlated with lower risk of esophagus and stomach cancer (GAO *et al.*, 1999). The protective role of this vegetables on stomach, esophageal and duodenal cancer development is likely to be associated with their antibacterial activity against *Helicobacter pylori*, a bacterium that plays a key role in the development of these types of cancer (O'GARA *et al.*, 2000; YOU *et al.*, 1989). Similar investigation conducted in Shanghai confirmed the link between increased intake of food rich in garlic, red onion, chive and leek and decreased risk of prostate cancer development (HSING *et al.*, 2002). Although these studies suggested that regular garlic and allium vegetables consumption reduce gastric cancer risk, KIM *et al.* (2018) found no statistically significant association between garlic intake and reduction of gastric cancer risk.

It was shown that consumption of red onion and garlic can inhibit colorectal cancer development. Six different studies showed that increased intake of raw or cooked garlic reduces the risk of colorectal cancer development from 10 to 50% (FLEISCHAUER *et al.*, 2000). In contrast, meta-analysis of eight different cohort studies showed that large intake of *Allium* vegetables does not reduce risk for colorectal cancer (ZHU *et al.*, 2014). TURATI

et al. (2014) found that high garlic intake is associated with a 15% reduction in colorectal cancer risk. These case-control studies showed a link between high intake of alliums and a reduction of colorectal adenomatous polyps.

YANG *et al.* (2009) found that the intake of raw onion and garlic can be protective against esophageal cancer in Taiwanese men. Other case-control studies reported that consumption of 7 or more portions of onions per week can be significantly protective against esophageal cell carcinoma (GALEONE *et al.*, 2006).

It has also been confirmed the association between consumption of *Allium* vegetables and lower risk for lung (SANKARANARAYANAN *et al.*, 1994) and brain cancer development (HU *et al.*, 1999). The case-control study was carried out among Iranian women with newly diagnosed breast cancer to investigate the effect of onion, garlic and leek on the breast cancer. The results suggested that the consumption of garlic and leek significantly reduced a risk for breast cancer development, while high consumption of cooked onion may be related with higher risk of breast cancer development (POURZAND *et al.*, 2016).

Several studies have reported that organosulfur compounds as well as flavonoids, such as quercetin 3,4'-diglucoside and quercetin 4'-monoglucoside can protect from cancer development in different tissues. They can activate or inactivate a wide variety of mechanisms to prevent cancer propagation. There are several proposed mechanisms of chemopreventive action of biologically active substances from *Allium* vegetables: inhibition of oxidative damage thanks to their strong antioxidant activity (LAWSON *et al.*, 1991; NUUTILA *et al.*, 2003; PERCHELLET *et al.*, 1990; SYED *et al.*, 2013), inhibition of cell proliferation and induction of apoptosis (ADAMS-CAMPBELL, 2011; ALTUNDAL *et al.*, 2016; ANTONY and SINGH, 2011; ATASHPOUR *et al.*, 2015; AQUILANO *et al.*, 2010; CHAN *et al.*, 2013; CHEN *et al.*, 2011; CHOU *et al.*, 2010; DUO *et al.*, 2012; HERMAN-ANTOSIEWICZ and SINGH, 2004; ICIEK *et al.*, 2012; KELKEL *et al.*, 2012; KIM *et al.*, 2013; KNOWLES and MILNER, 2000; LEE YJ *et al.*, 2015; LEE WJ *et al.*, 2015; LEE *et al.*, 2010; NAGARAJ *et al.*, 2010; NIU *et al.*, 2011; PERCHELLET *et al.*, 1990; REN *et al.*, 2015; RUSSO *et al.*, 2014; VIDYA PRIYADARSINI *et al.*, 2010; YI *et al.*, 2010a,b), inhibiting of procarcinogens activation by their effect on cytochrome P450 (CHEN *et al.*, 2009; CHOI *et al.*, 2011; KUMAR and PANDEY, 2013; WARGOVICH, 2006; YANG *et al.*, 2001b), inhibiting DNA damage (anticlastogenic effect) (FREDOTOVIĆ *et al.*, 2014; HAZA *et al.*, 2011; KHANUM *et al.*, 2004; LAU *et al.*, 1990), inhibition of lipoxygenase and cyclooxygenase activity (anti-inflammatory effect) (ADÃO *et al.*, 2011; ALI, 1995; BELMAN *et al.*, 1989; BYUN *et al.*, 2013; DIRSCH and VOLLMAR, 2001; CHANG *et al.*, 2005; ELBERRY *et al.*, 2014; PARK, 2011; PERCHELLET *et al.*, 1990; PRASANNA and VENKATESH, 2015; ROSE *et al.*, 2005; WANG *et al.*, 2012). Additional studies need to be done to confirm the chemopreventive effect of these vegetables as well as the exact mechanism of their action.

4. CONCLUSIONS

For centuries, *Allium* vegetables have been very suitable ingredients in a wide variety of cuisines worldwide. They produce specific chemicals, mostly organosulfur compounds and flavonoids that give them the unique taste and smell but also are responsible for their biological activity. Beside these main active compounds, they possess small amounts of saponins which contribute to the health benefits of these vegetables. The antimicrobial activity of *Allium* species has been proved against a wide range of bacteria, fungi and yeasts. Numerous studies confirmed them as potent antioxidants capable to catch and inactivate free radicals and therefore prevent oxidative cell damage. Strong antioxidant activity was found to be related mainly with sulfur-compounds as well as flavonoids.

Different studies have indicated that *Alliums* possess anti-inflammatory properties via scavenging reactive oxygen species and through the inhibition of proinflammatory cytokines expression. *Alliums* possess remarkable antiproliferative activities against different cell lines which is directly related with their anticancer activities. There are proposed several potential mechanisms for their anticancer action, but it is necessary to perform more research to confirm them as effective anticancer agents.

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