

## Gastroprotective Activities of *Buddleja scordioides*-Role of Polyphenols against Inflammation

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Received date: Jun 13, 2016; Accepted date: Aug 25, 2016; Published date: Aug 29, 2016

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### Abstract

Medicinal plants show great interest today because of its multiple physiological effects. They contain a diversity of chemical compounds, phytochemicals, with demonstrated important biological activities. *Buddleja scordioides* Kunth is a plant that shows a wealth of important phytochemicals, which could contribute towards the prevention of various health problems such as gastrointestinal disorders. The main causes of gastrointestinal pathology are mediated by inflammatory processes caused by several factors. *B. scordioides* HBK (KUNTH) is commonly used for the treatment of diarrhea and stomach pain (colic). Several studies shown presence of flavonoids such as rutin, quercetin and quercetrin and kaempferol (also found in *Buddleja* genus). Other isolated compounds include some hidroxycinnamic and hidroxibenzoic acids, verbascosides, siringin, some iridoids, sesquiterpenes and fenilpropanoids. All of them related with anti-inflammatory activity. The present review is an opinion of the state of art anti-inflammatory activity of *B. scordioides* and gastrointestinal disorders.

**Keywords:** Anti-Inflammation; *Buddleja scordioides*; Gastroprotection; Phytochemicals

### Introduction

Medicinal plants show great interest today because of its multiple physiological effects. They contain a diversity of chemical compounds, phytochemicals, with demonstrated important biological activities. These compounds are produced by the secondary metabolism of plants, which have evolved from different biotic or abiotic factors, and used by the plant for defense or survival. However, multiple studies on these compounds have proven beneficial to human health [1].

Phytochemicals have multiple properties such as antioxidant and anti-inflammatory, which can be used as a preventive means to protect against the development of health problems. They may interact with molecules that can inhibit the genesis of this type of pathologies or conversely, interact with biomarkers that enhance the protective capabilities of the organism.

Medicinal properties of many plants are mainly attributed to the presence of flavonoids, but these effects may also be promoted by other organic and inorganic compounds such as coumarins, alkaloids, terpenes, tannins, antioxidant phenolic acids and micronutrients, for example, Cu, Mn and Zn. *Buddleja scordioides* Kunth is a plant that shows a wealth of important phytochemicals, which could contribute towards the prevention of various health problems such as gastrointestinal disorders. Nowadays these diseases have been considered a health problem around the world due to its high incidence.

### Gastrointestinal disease and inflammatory response

Gastrointestinal diseases are one of the most common health problems that affect people of all ages and social condition, although the most vulnerable groups are children and the elders.

In Mexico in 2008, the incidence of ulcers, gastritis and duodenitis were larger than the states of Nayarit, Tabasco and Durango (3396.11, 3212.11 and 2193.78 cases per 100,000 population, respectively) [2]. In general, these problems are associated with inflammatory processes, which are part of a non-specific response of tissues that occurs in reaction to any type of injury, which is an immune response to pathogens, damaged, irritating cells, etc. [3].

The main symptoms of inflammatory processes are: Redness, heat, pain and tumor and also these symptoms can cause high cellular metabolism, vasodilatation, and high blood flow [4]. In some diseases the inflammation process under normal conditions is restrictive; it becomes chronic dysfunctions that develop subsequently. In inflammatory processes, it can be distinguished two steps of inflammation: 1) Acute inflammation that is the immediate response to vascular changes, where widespread effects of inflammation mediators cause pain, heat and swelling; these symptoms are usually short-lived. 2) Chronic inflammation is self-prolonged that and can last for weeks, months and even years, and can be developed as a result of recurrent or progressive acute inflammation [5].

The main causes of gastrointestinal pathology are mediated by inflammatory processes caused by invading microorganisms ingested in the diet, use of medications that hurt the mucosa such as non-steroidal anti-inflammatory drugs (NSAIDs), milk and dairy fats, alcohol, stress and nervousness are responsible for many digestive disorders [6]. Their presence of symptoms is varied, may include stomach or abdominal pain accompanied by cramps, diarrhoea, dehydration, abdominal bloating, increased intestinal gas, lawn blood, fever, tires, loss of appetite and weight loss, weakness and constipation, among others [7].

Once developed an inflammatory process focused on the gastrointestinal tract, the mucosa in charge of maintenance and integrity causing activation of immune cells, which begin to produce different proteins (cytokines) by expressing different molecules in

response to the inflammatory process [8]. Interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF $\alpha$ ) have an important role in gastric inflammation because they are the main mediators in the early inflammatory response [9]. They can stimulate the production of proteins to mobilize neutrophils to the damaged place with problems, to direct the hypothalamus to a febrile response and to increase the number of adhesion molecules in the vascular epithelium. Other cytokines observed in gastric inflammation are IL-8, IL-6, IL-18 and INF $\gamma$  [10].

One of the earliest symptoms present in a disease of the gastrointestinal tract is the presence of ulcers, which are caused by an imbalance between aggressive and protective factors in the gastrointestinal tract as affected by issues such as the secretion of acid-pepsin, the mucosal barrier, mucus secretion, blood flow, cell regeneration, and prostaglandins [11-13]. Some additional causes are stress, smoking, nutritional deficiencies, hereditary bias, *Helicobacter pylori* infection and ingestion of non-steroidal anti-inflammatory drugs (NSAIDs), are factors that may increase the incidence of gastric ulcers [14].

Two types of gastrointestinal pathologies, Crohn's disease and ulcerative colitis are highlighted. Crohn's disease is one of the two major diseases of the gastrointestinal (GI) tract, known as inflammatory bowel diseases (IBD). The other, ulcerative colitis affects the large intestine, which includes the colon and rectum, is a disease that causes inflammation or swelling and irritation in any part of the gastrointestinal tract. It most often affects the ileum which is the last portion of the small intestine [15,16].

Crohn's disease is a chronic inflammation that may cause scar tissue to form in the lining of the intestine. Once the scar tissue builds up, the tube can be reduced, which makes food and the reasons go more slowly through the digestive tract, which can cause pain, cramping and diarrhea [17]. Its causes are ignored, however, it is believed that the immune system is involved, because during the defense against bacteria or viruses, white blood cells accumulate in the intestinal lining. White blood cells cause chronic inflammation that causes ulcers, wounds and lesions in the intestine. The most common symptoms are manifested as abdominal pain, diarrhea, bleeding in the rectum, weight loss, fever, etc. [18].

Ulcerative Colitis is an inflammatory bowel disease that despite being controlled with medication and in severe cases is treated through surgery that may conduce to complications and death [19]. Ulcerative colitis is characterized by pain and inflammation in the stomach and can be triggered in colon cancer [20].

These inflammatory processes may activate some biomarkers like cyclooxygenases, which are enzymes that allow the body to produce prostaglandins from arachidonic acid. This type of enzymes can act as dioxigenase or peroxidase as they are peripheral membrane proteins. It has two isoforms [21]. COX1, present in most tissues such as stomach synthesizing prostaglandins and perform maintenance of the gastric mucosa, which regulates proliferation of normal cells and intervenes indirectly in physiological processes such as protection and neutrophil migration to the epithelium. And COX2, which is formed from an increase of prostaglandins in tissues where an inflammatory response occurs. It is expressed after induction of inflammation caused by erosion of the mucosa [22].

An induction of COX2 activates inducible nitric oxide synthase (iNOS), as well an over expression of cytokines (Tumor necrosis factor (TNF), interleukin 1, 6, 8) as well alterations in expression of RNA

fragments, which plays a role in inflammation process product of oxidative stress [23].

Cytokines are small proteins that play an important role in cell signalling because they have an important effect on the behaviour of cells around them. The most important are interleukin 8, interleukin-1 $\beta$  and TNF $\alpha$ , which are considered to start and perpetuate the inflammatory process. Interleukin 8 (IL-8) occurs in several cell types such as monocytes, T lymphocytes, neutrophils, macrophages, endothelial cells and gastric cancer cells [24,25]. Neutrophil infiltration into sites of inflammation is one of the markers of acute inflammation, they release lysosomal enzymes and to increase the expression of factors such as CR-1 to adhere to endothelial cells [26]. Also induces the expression of NFK $\beta$ , ICAM-1, VCAM-1 and COX-2.

IL-6 is a pleiotropic cytokine capable of regulating proliferation, differentiation and activity of a variety of cell types and plays a pivotal role in immune system homeostasis [27]. In particular, IL-6 plays a major role in acute phase response, in the balancing of the pro-inflammatory/anti-inflammatory pathways and in the stress response besides affecting the immune response [28]. Also induces the expression of transcriptional factors, adhesion molecules and cyclooxygenases.

Interleukin 1 beta (IL-1 $\beta$ ) is a cytokine produced by macrophages which is activated by inflammatory process, which is regulated by the expression of transcriptional factors as NFK $\beta$ . It is one of the major mediators of cell communication with the angiogenic inflammatory area and regulate in a positive way the synthesis of pro-angiogenic factors such as IL-8 [29-31].

TNF $\alpha$  is one of the largest of pro-inflammatory cytokines and routinely occur at sites of inflammation. Their biological functions, which are regulated by the high similarity of binding to receptors found in a large number of cell types [32]. The effects of receptor binding, include inhibition of metabolism of triglycerides in adipocytes, activation of neutrophils in the inflammatory or ulcer process, activation of multiple pathways of signal transduction, kinases and transcription factors [33].

These processes are caused by oxidative stress, which is caused by an imbalance between reactive species and antioxidant capacity, the most important species produced in inflammatory response are reactive oxygen species (ROS) which are involved not only kinetic and molecular changes of enzymes, co-substrates, cofactors and antioxidant molecules, but also the power of genes and changes in the protein expression. Oxidative stress can be efficient and limit its damage; otherwise it may be inefficient and unable to avoid promoting damage, which may depend on the degree of defense or lack of response from the elements of the antioxidant systems [34]. Also oxidative stress plays an important role in the modulation of messengers that regulates essential cell membrane functions, which are vital for survival. It affects the redox status, activation of protein kinases which plays in cellular responses such as activation, proliferation and differentiation, as well as various other functions [35-37].

However, they are very reactive since spread to decrease in order to achieve stability, for which the antioxidants tend to release an electron to donate to radical for the purpose of stabilizing [38]. Reactivated oxygen species may contribute to the generation and maintenance of chronic pain. This includes free radicals and oxygen derived molecules of biological interest with high reactivity that is capable of producing free radicals in the human organism [39].

These reactive species are molecules that reactivate and attack regularly to the body through redox reactions and are carried out as a normal part of metabolism or pathology. There are multiple sources for ROS generation, especially mitochondrial respiration, activation of polymorphonuclear leukocytes, arachidonic acid metabolism, catalysis by the release of iron and copper and enzymatic action.

The ROS effects can be manifested itself in different ways. The damage can be shown as peroxidation chains of unsaturated lipids, DNA modification (base modifications, it breaks one strand, crosslinked protein-DNA), loss of carbonylation in proteins, causing the enzyme activity to be lost [40].

Oxidative stress and inflammatory process activates immune cells as a defense system [41-43]. This is due to inflamed cells produce some arachidonic acid metabolites, cytokines and citocines causing recruitment of immune cells directing them towards damage site, producing more reactive species because it is the way to attack the cells of the immune system [23]. In gastrointestinal pathologies, once the gastric mucosa is degraded and the infiltration of immune cells is present, these cells begin an uncontrolled production of reactive oxygen species, which result in an unrestrained enhancement of the oxidative stress status.

Once oxidative stress promotes the inflammatory process, signaling cascades that favor an increase in these processes are activated by transcriptional factors such nuclear factor k-B (NFK $\beta$ ). This undergoes translocation from cytoplasm to the nucleus in response to an extracellular signal. This translocation induces its ability to bind to DNA, leading to transcriptional up-regulation of the expression of many genes related to inflammation and immunity. Thus, NFK $\beta$  seems to be involved in development and aggravation of many diseases as gastrointestinal. This process requires a signal derived from ROS, TNF $\alpha$ , IL-1 $\beta$ , IL-6, which enhances the activation of NFK $\beta$  [35-37].

### Antioxidants as disease regulators

An antioxidant is any substance that when present at low concentrations compared to an oxidizable substrate delay or inhibit oxidation of that substrate [44]. There are several lines of defense in the body, of which protection against formation of reactive oxygen species (ROS) is the best. However, when performed ROS in the body, substances that can be used to improve the oxidative state.

When the balance between prooxidant and antioxidant in the human body has lost uncontrolled production of free radicals, causing antioxidant defenses to be inadequate, generating an increase of oxidative stress causing cellular damage that can lead to death [45].

Oxidative stress can occur by numerous causes. Thus, poor nutrition can severely deprive people of minerals such as Cu<sup>2+</sup>, Mn<sup>2+</sup>, [Zn<sup>2+</sup>]<sup>2+</sup> and several vitamins such as ascorbic acid and riboflavin needed for antioxidant defense. Some drugs and toxins cause oxidative stress during their metabolism [46].

A free radical is a molecule that has an unpaired or odd electron in the outer orbital, giving a spatial configuration that generates a high instability [47]. This instability gives them the ability to capture an electron from any other molecule in its environment, causing the affected structure to be unstable. Thus they can be established as chain reactions by means of conveyors which are oxidized or reduced. For example, in DNA damage to nucleic acids produces modified bases, which has serious consequences either on the development of

mutations and carcinogenesis or loss of expression by damage to specific genes [48].

Oxidizing species at high concentration causes more damage than the cell can repair, thus, death eventually ensues. Even if there is a balance between oxidants and antioxidants, it may leave an unrepaired damage point that may not immediately alter the metabolism of cells [49]. In the case of DNA this may be of great importance because damage can accumulate and inherited by following cell generations resulting altered genotypes and functionally deficient cells [50].

Among the most studied radicals are reactive oxygen species (ROS). These are highly reactive molecules that attack the body regularly through redox reactions and occur as a normal part of metabolism or pathology [47]. The main reactive oxygen species (ROS) are: Molecular oxygen (O<sub>2</sub>), ozone (O<sub>3</sub>) and oxygen species which are partially reduced; that is, superoxide anion (O<sup>2-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroperoxyl (HO<sub>2</sub>) and hydroxyl radical (OH). These species are the result of the excitation rupture of O<sub>2</sub> and are more reactive than O<sub>2</sub> in its ground state [34].

There are multiple generators of ROS, especially mitochondrial respiration, activation of polymorphonuclear leukocytes, metabolism of arachidonic acid, release catalysis of iron and copper and enzymatic action. Also exogenous factors, some controllable by the individual and others, such as toxic habits and environmental pollution [40].

Some studies in biological activities on herbal sources have shown that some compounds present in plants or in normal or formulated foods (such as preservatives) can stimulate the antioxidant defense system in humans, neutralizing the damage caused by free radicals. This may have beneficial effects against health problems such as gastrointestinal, respiratory and cardiovascular [51].

Many medicinal plants are currently used in the treatment of modern diseases or better known as diseases of our civilization. Many of those diseases are caused by stress of our lifestyle in developing countries, where also several side effects are caused by the indiscriminated use of pharmaceuticals that can produce stress, ulcers, headaches, skin allergies, etc. [52].

Antioxidants are substances which retard oxidation, inhibiting free radical reactions and play an important role in prevention of several diseases. Of the many classifications of antioxidants, it is more accepted divide them into: Exogenous antioxidants, which enter through the food chain; and Endogenous antioxidants, which are synthesized by the cell itself [53].

In the survival of plants all metabolic functions are universally recognized as critical and have been called together primary metabolism. However, plants are almost exclusive possessors of other metabolic pathways by synthesizing an extremely wide range of substances called secondary metabolites [54].

Plants, vegetables and herbs used in traditional medicine have gained wide acceptance as the main sources of bioactive phytochemicals. For this reason, information about the antioxidant properties of natural products has become prominent lately in the fields of nutrition and the development of nutraceuticals.

Polyphenols are compounds that plants produce to protect themselves from other organisms. Dietary polyphenols shows important roles in human health. High intake of sources rich in polyphenols, has been linked to lowered risks of many chronic diseases including cancer, cardiovascular disease, chronic inflammation and

many degenerative diseases [55,56]. Recent studies have revealed that many of these diseases are related to oxidative stress from reactive oxygen and nitrogen species.

These polyphenols product of their secondary metabolism which the plant uses to defend, can function as exogenous antioxidants because they can help delay, inhibit or prevent the oxidation process by acting as free radical scavengers decreasing the process known as oxidative stress. In this sense supplement with antioxidants it is essential to prevent and delay the possible consequences of oxidative stress [57,58]. This ability is made possible by its ability to trap free radicals, in which the polyphenols can break uncontrolled free radical generation, on the other hand can regulate the enzymatic activity (superoxide dismutase, catalase, glutathione peroxidase) or chelating metals involved in the production of free radicals [59,60].

The current interest for the study of secondary metabolism has various shades. On one hand, almost all of the known secondary metabolites have some kind of activity, the so called antibacterial, antioxidant activity or the anti-cancer, among others. On the other hand, many metabolites are part of the defense mechanisms against attack by herbivores and pathogens and the study of plant-herbivore interaction allows viewing in the near future the development of vaccines for the protection of plants of economic interest [61].

Finally, the distribution of particular types of these secondary compounds within groups of related taxonomically plants and chemical species, based on the secondary metabolism is established between organisms of various trophic levels. They are looking to find evolutionary relationships between different organisms that synthesize these substances and to understand the establishment of the ecological balance of ecosystems [61].

In a very general manner, secondary metabolites are classified according to their origin into three groups: Phenols, terpenes and secondary compounds. For purposes of this review dominating phenolic compound, also called phenols or plant polyphenols, which are substances that possess at least an aromatic ring and a hydroxyl substituent in its chemical structure, i.e., a phenolic group.

The same phenol as a natural product in the plant kingdom, but is more common phenolic compounds having two or more hydroxyl groups. Of all the secondary metabolites, phenols are the most widely distributed within the plant kingdom and perhaps the most diverse [62].

The diversity of plant phenols is reflected in the classification made Harborne [63]. This author acknowledges 13 phenolic groups identified by the basic skeleton of the carbon atoms as the compound C6 are simple phenols; Or C6-C1 Phenolic acids; C2-C6 including phenylacetic acids and acetophenons; C3-C6 acids including, hydroxycinnamic phenylpropenes, coumarins, and cromones isocoumarins; C4 or C6-naphthoquinones; C6-C1-C6 or xanthenes; C6-C2-C6, including stilbene and antroquinones; C6-C3-C6 or flavonoids; (C3-C6) 2 or lignans; (C6-C3-C6) 2 or bioflavonoids; (C6-C3) No lignins; (C6) 6 or catecholamines; and (C6-C3-C6) No flavolans, also called condensed tannins.

Phenolic compounds originates from the shikimic acid pathway Hrazdina [64] calls the aromatic compounds formed in three segments: The shikimate, which produces the aromatic amino acids as phenylalanine, tyrosine and tryptophan; that of pheilpropanoids occurring cinnamic acid derivatives, which in turn are precursors of flavonoids and lignins and; Finally, the flavonoids that produces the

diversity of compounds of the latter group. From all this diversity of phenolics, flavonoids (C6-C3-C6) are those which have the widest distribution within the plant kingdom [65] and are the most abundant and diverse. In a naturally flavonoids can be in two forms, together with a glycoside or without a sugar residue in its molecule. The first is 8 seconds glicosidade shapes and forms are called aglycone (Figure 1).

In aglycone form, flavonoids have a benzene ring condensed with a heterocycle ring and joined a phenyl ring in position 2.

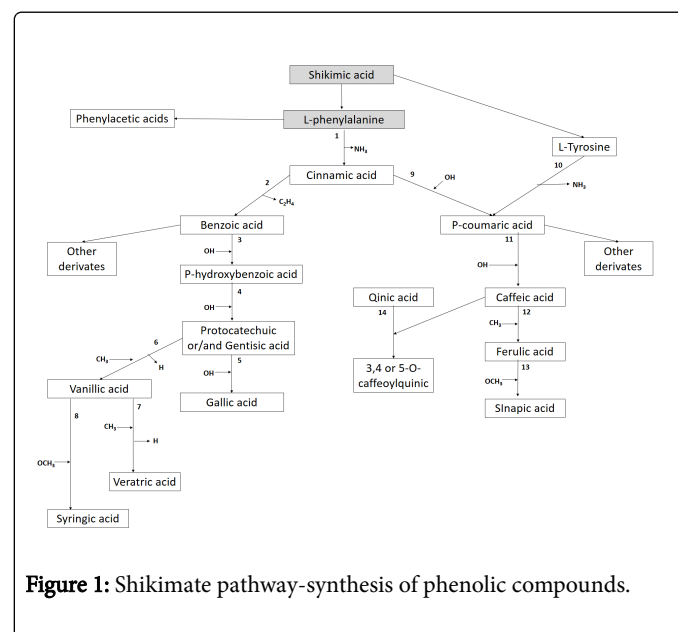


Figure 1: Shikimate pathway-synthesis of phenolic compounds.

Polyphenols have been described to have beneficial effects in several acute and chronic disorders [66,67]. That's why epidemiological and experimental studies have been focused on the anti-inflammatory activity of dietary polyphenols [68,69].

There are many mediators, such as vasoactive amines like histamine 5; some adhesion molecules: Intercellular adhesion molecule 1 (ICAM 1), vascular adhesion molecule 1 (VCA M 1), selectins; lipid-derived eicosanoids: Prostaglandin E2 (PGE2), prostaglandin I2 (PGI2), leukotriene B4 and C4 (LTB4, LTC4); cytokines: Tumour necrosis factor (TNFa), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10) and chemokines: interleukin-8 (IL-8), monocyte-chemoattractant protein-1 (MCP-1), that coordinates the events of acute inflammation, regulate vascular changes and inflammatory cell recruitment [68-72]. It has been shown that phenolic compounds may interact with cells by a wide spectrum of molecular targets.

The molecular mechanisms involved in the anti-inflammatory activities of polyphenols have also been suggested to include: The inhibition of pro-inflammatory enzymes, such as cyclooxygenase (COX-2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS), the inhibition of kinases, nuclear factor-kappa B (NF-κB), and the activation of phase II antioxidant detoxifying enzymes (Superoxide dismutase, catalase, glutathione peroxidase), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), serin/threonin protein kinase Akt/PKB as well as iv) the modulation of several cell survival/cell-cycle genes [73-75].



### Gastroprotective activities of *Buddleja scordioides*

*Buddleja* or *Buddleia* (Figure 2) genus belongs to the Solanaceae family. It is a genus native to Asia, Africa, North and South America that comprises about 100 species, 50 are distributed in the United

States, of which 16 are in Mexico [76]. There are some similarities between species of the genus *Buddleja* in respect to their medicinal uses. This may indicate the presence of common compounds with a particular pharmacological action.

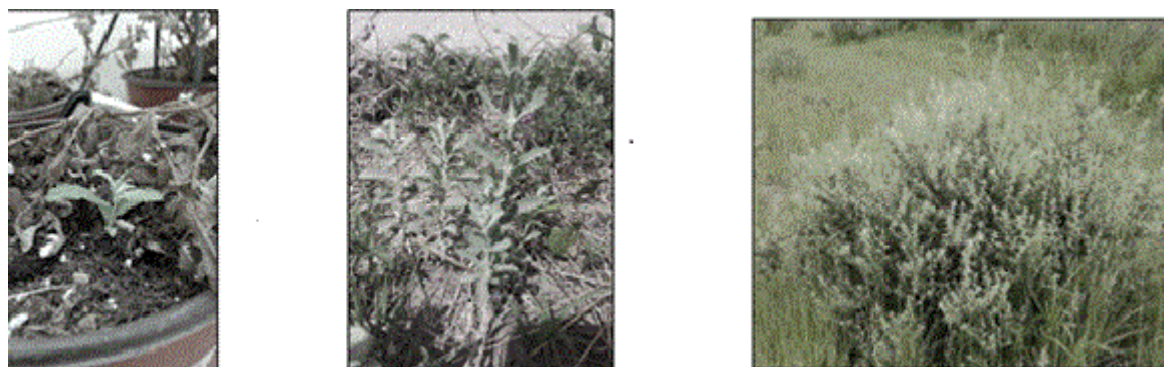


Figure 2: *Buddleja* or *Buddlia*.

A pattern emerges on the composition of these plants: flavonoids and glycosides iridoids be the main secondary metabolites that have been isolated so far, and are common in the species of this genus [77] because of this phytochemical composition of *Buddleja* genus has been thoroughly investigated; a valuable review this chemical composition as well as some of their biological activities have been published by Houghton [77,78].

Multiple studies have been reported for these plants, including multiple biological activities such as liver protection, anti-inflammatory, analgesic, antipyretic, anti-cascades, anti-rust, hypoglycemic activities, neuroprotective, antimicrobial, etc. They are also used in folk medicine for its potential healing and diuretic effects [79-82].

In particular, *B. scordioides* HBK (KUNTH) is commonly known as brush, royal sage, butterfly bush, kill, and salver. It is a very wavy and rough aromatic and branched bushy plant up to 1.5 m tall, with elongated leaves. The flowers are yellowish green or yellow. The fruits are spherical and have yellow seeds [83]. It grows in dry, semi-dry climates, between 1800 and 2300 mosl. It grows along roadsides, in disturbed vegetation associated with pine oak-heath forests.

In some areas this plant is considered parasite. However, this plant is used for the treatment of diarrhoea, stomach pain (colic) and gastrointestinal disorders [84]. Also in traditional medicine, it has been used as infusion for the treatment of burns, ulcers and internal and externally for wound healing [84].

Aqueous extracts of *Buddleja* have been used for various types of diseases [83]. The Tepanecas, an indigenous group of Guerrero, Mexico, has used tea leaves of *B. scordioides* for the treatment of skyn injuries. People of Aguascalientes (Mexico), use decoctions of *B. scordioides* leaves for the treatment of ulcers [84]. In Durango and Guanajuato, its medicinal uses include treatment of digestive problems, mainly stomach pain and diarrhea. Besides it is being used as eupéptica. For this purpose, it is recommended to take the infusion of branches or roots, which, also seeks advice to boil milk for children to eat when they have colic discomfort.

Houghton and Mensah [78] mention that the most important compounds in *Buddleja* are flavonoids. These phytochemicals are associated with their anti-inflammatory activity and their presence can help the healing process or to the inhibition of certain cytokines or molecules associated to accession of gastrointestinal problems.

Some flavonoids such as rutin, quercetin and quercetrin have been isolated and identified in the leaves of *B. scordioides*; they are involved in the inhibition of the colitis processes [83]. Another flavonoids as kaempferol (also found in *Buddleja* genus) inhibits the activity of the morning arachidonate-5-lipoxygenase, a key enzyme in prostaglandin synthesis [85]. Other isolated compounds include some hidroxicinnamic and hidroxibenzoic acids, verbascosides, siringin, saikogenin, 3,23,28 trihidroxioleane 11, 13 (18) diene per-acetate-3-O- $\alpha$ -L-ramno-piranosile-(1 $\beta$ 4)- $\beta$ -D-gluco-piranosile-[(1 $\beta$ 3)- $\beta$ -D-glucopiranosile-(1 $\beta$ 2)]- $\beta$ -D-fuco-piranosile 3,23,28,(18) diene trihidroxioleane 11, 13, 3-O- $\beta$ -L-ramno-piranosile-(1 $\beta$ 4)- $\beta$ -D-gluco-piranosile-(1 $\beta$ 3)-[ $\beta$ -D-gluco-piranosile-(1 $\beta$ 2)]- $\beta$ -D fuco-piranosiel-3, 16, 23, 28- tetra-hidro-xioleane-11,13(18)-diene and per-acetate *buddle-jasaponiea* [86]. Some iridoids, sesquiterpenes and fenil-propanoids [77] have also documented their presence in *B. scordioides*.

There have been various studies regarding the antioxidant and anti-inflammatory activity of the *Buddleja* species [79]. However, results may vary, as the phenolic compounds are naturally variable in relation to its concentration due to some factors such as location, type of soil, the incidence of light, amount of water, etc.

The presence of some phenolic acids such as chlorogenic, ellagic and caffeic acids, and their derivatives have found a significant level of gastric mucosa protection because of activated adhesion molecules that regenerate and maintain the epithelial wall, which ensures inhibition of the colitis process [87].

Also *B. scordioides* has shown significant activity in modulating enzymatic defense system, mostly on the activity of glutathione peroxidase, which is responsible for the removal of hydrogen peroxide, an important molecule in the development of oxidative stress. This important modulation may be due to peroxide, which was neutralized

by the antioxidant compounds present in herb sources rich in phenolics [87-89].

Among the main anti-inflammatory activities found in *Buddleja* species, it is necessary to emphasize the interaction with cyclooxygenases. Backhouse [89] document the anti-inflammatory activity on COX-2 in extracts of *B. globosa*, and attributed the activity to the presence of verbascósido and luteolin-7-glucoside. Mutoh [90] report that expression of COX-2 is suppressed by flavonoids and that this activity is related to the number of hydroxyl groups present in the ring B and the presence of an oxo group at position 4 of the C ring, as in quercetin. This is important since the constitutive cyclooxygenase (COX-1) is responsible for the protection of the gastrointestinal tract, while the inducible form (COX-2), a mediator inflammation, is considered in both key enzymes, involved in formation of bicyclic product proxides oxygenation of polyunsaturated fatty acids.

Gretzer [91] found that the damage was observed in the gastric mucosa of healthy stomachs only when expression of both COX-1 and COX-2 is inhibited. An important intermediary in inflammation is nitric oxide (ON), reducing platelet aggregation and adhesion; it inhibits several features of inflammation induced by white blood cells, and serves as a regulator of leukocyte recruitment [92]. Blocking the production of nitric oxide under normal conditions, promoting the formation of leukocyte rolling and adhesion in the post-capillary vessels, and delivering exogenous NO, reduces leukocyte recruitment in acute inflammatory processes. Thus, overproduction of nitric oxide from induced nitric oxide synthase (iNOS) is a compensatory mechanism that decreases leukocyte recruitment in inflammatory responses.

Therefore, it should be noted that studies on *Buddleja* extracts evaluated in animal models subject to gastrointestinal damage, reflect significant activity above the negative control without damage, reflecting an apparent protection of nitric oxide caused by a decrease in nitrites, which are reactive metabolites from NO [87,92,93]. NFK $\beta$  is one of the most important regulatory molecules in inflammation expression. The synthesis of cytokines such as TNF $\alpha$  are IL1 $\beta$ , IL6 and IL8 mediated directly by NFK $\beta$  and the expression of COX2 [94,95]. Once this marker has expressed the signaling cascade of the inflammatory process begins and can damage the cell [96].

The presence of flavonoids in species of *Buddleja* genus as several authors have shown their impact in reducing NFK $\beta$  in rats with chronic disease [97] and in different in vitro assays inhibiting the onset of TNF $\alpha$  [98-100]. Some researchers have associated this behavior with the inhibition factor (AP-1) [101,102]. Finally, administration of different extracts of this specie can guarantee a considerable inhibition of this marker, which can trigger an inhibition of pro-inflammatory cytokines and to begin a controlled anti-inflammatory molecules synthesis.

## Conclusion and Outlook

The interest in studies on functional foods has gained increased relevance due to the multiple biological effects that are shown by various food sources, likewise the study of so-called medicinal plants we may give a wide perspective on how such sources favor prevention or elimination of major health problems for the population and particularly focused on the gastrointestinal disorders.

The use of plants from the *Buddleja* genus offer us a matrix rich in compounds of phenolic nature, which can not only participate as an

important source of antioxidants, but also this ability shows important effects on target molecules, which favor the occurrence of gastrointestinal diseases.

It is also important to continue studies of this nature, as they could offer a world of possibilities to the prevention of other related diseases that affect the population today.

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