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Review article

The bitter Asteraceae: An interesting approach to delay the metabolic syndrome progression

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A B S TR A C T

The prevalence of metabolic syndrome (METS) directly correlates with the prevalence of obesity, and it is associated with several other risk factors. Among them, chronic inflammation, oxidative stress and insulin resistance might be reduced in order to delay the progression of METS. The first management of METS involves physical exercises and a suitable diet. Many Asteraceae are plants commonly consumed. The bitter Asteraceae known for their health effect are traditionally used as bitter drinks. Their particularly rich contents in sesquiterpene lactones and hydroxy-cinnamic acids mainly in caffeoyl derivatives, confer to these plants good anti-METS potential. These compounds are known for their antioxidant, anti-inflammatory and insulin sensitizing effects and confer to bitter Asteraceae the potential to be good candidate products to delay METS.

1. Introduction

Metabolic syndrome (METS) is a cluster of metabolic abnormalities diagnosed when three of the following five risk factors are present: obesity with enlarged waist circumference, hypertriglyceridemia, a decrease in HDL cholesterol, elevated blood pressure and elevated fasting blood glucose [1]. METS affects between 20% and 30% of adult populations in most countries. Its prevalence increases with age from 10% in 20–29 years old individuals reaching 45% in adults 60–69 years old [2]. The prevalence of METS is 5% among normal-weight individuals, 22% among overweight subjects, and 60% among obese people. The prevalence is high in countries such as the United States (US), with 35% of all US adults (50% of individuals over 60 years old) estimated as having METS [3].

The causes of the METS are complex and result from an association between genetic, environmental and epigenetic factors. Reaven was the first to point out the important role played by insulin resistance in the syndrome etiology [4]. The abdominal obesity marked by an increase in blood free fatty acids promotes pro-inflammatory adipokines and cytokines production such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), leading to a chronic low-grade inflammation [5,6]. An overproduction of oxygen reactive species (ROS) in adipose tissues leads to the loss of their redox homeostasis and contributes to a pro-inflammatory state [7–10]. Obesity and associated chronic inflammation initiate a state of insulin resistance through disruption of the insulin signaling cascade [6,7] causing a pernicious circle (Fig. 1) that will lead to type 2 diabetes in the medium term.

The initial management of METS involves lifestyle modifications, including physical activities and diet management, such as low-calorie diets (LCDs), liquid meal replacements (another method for facilitating adherence to LCD), and very-low-calorie diets (VLCDs) [11]. The last ones are recommended for individuals who failed to lose weight with an LCD. However, this may not be enough to effectively delay the syndrome progression and justifies diets based on foods known for their anti-METS virtues acting on preliminary events of METS. Plants containing active substances against oxidative stress, inflammation and insulin resistance might be used to break the pernicious circle (Fig. 1).

Many reports have underlined the anti-METS beneficial effects of numerous plants normally consumed. This led to a lists of beneficial vegetables potentially reducing or delaying the effects of type 2 diabetes [12]. Coffee is often cited for its antioxidant and insulin-sensitizing effects that confer it an antidiabetic action [13,14]. In their review, Rochlani et al. [15] compiled the literature data about anti-METS effect of 14 plant species and their compounds. They emphasize the correlation between the anti-METS potential and an antioxidant, anti-inflammatory effects and/or an insulin sensitizing action in these plants. Among the studied vegetals, fenugreek (Trigonella foenum-graecum, Leguminosae), onion (Allium cepa, Liliaceae), cinnamon (Cinnamomum verum, Lauraceae), turmeric (Curcuma longa, Zingiberaceae), and cumin (Cuminum cyminum, Apiaceae).
The antioxidant capacity of polyphenols present in plants and vegetables has attracted interest for the management of METS [16]. Plant-based foods and beverages contribute to a large polyphenol intake in many world diets. Coffee and tea are known as a important source of polyphenols in diet [17]. The hydroxycinnamic acids constitute a group of polyphenols largely cited for their anti-METS effects [18,19]. Among them caffeeic acid and derivatives named caffeyl derivatives by Fraisse et al. [20] are known as efficient antioxidants. In addition, caffeyl derivatives are also considered as cardio- and hepatoprotective [21–23], antihypertensive, anti-inflammatory [24–26], anti-hyperglycemic and anti-diabetic [27–30].

Asteraceae is a botanic family widely described for its high content in hydroxycinnamic acids, particularly caffeyl derivatives. The mono-, di- and tri-caffeoyl quinic acids (CQAs) represent the most abundant part of them, while in some Asteraceae species, the dicafeoyl tartaric acid, namely chicoric acid, is majorly produced [20]. Traditional medicine attributes hepatoprotective function to the bitterness of Asteraceae [31] and an antihyperlipidemic properties [32]. Among Asteraceae, the bitter Asteraceae containing a high level of sesquiterpene lactones, which contribute, like caffeyl acid, derivatives, to the bitterness, constitute a particular class in the Asteraceae family [33]. In addition to organoleptic properties, sesquiterpene lactones also possess anti-inflammatory properties [34] and were demonstrated to be beneficial for the management of diabetes and obesity [29]. This particular content rich in both caffeoyl derivatives and sesquiterpene lactones in bitter Asteraceae supports the hypothesis of a plant family particularly beneficial to delay the progression of metabolic syndrome. In order to consider this bitter Asteraceae anti-METS potential we have built a list of the most well known bitter Asteraceae and compiled the associated literature data. This should allow the attribution of antioxidant, anti-inflammatory and/or an insulin-sensitizing effects for each of them in relation to their caffeyl derivatives contents. This analytical approach is intended to help develop credible preventive anti-METS diets based on the consumption of bitter Asteraceae species.

2. Bitter Asteraceae species

2.1. Artichoke (Cynara scolymus L.)

Artichoke is one of the oldest known cultivated plants in the world. It has a high bitter index and is used as a food and medicinal remedy. This Asteraceae possesses several virtues as antioxidant, choleretic, hepatoprotective, as well as lipid-lowering effects [35]. Polyphenolic constituents from artichoke extracts are widely recognized to be potent antioxidants and anti-inflammatory [36–38]. Moreover, an artichoke hydro-ethanolic extract reduced hyperglycemia in diabetic streptozotocin rats [39]. Artichoke contains chlorogenic acid in great quantity [37] about 39% of the total CQAs.

2.2. Bitter leaf (Vernonia amygdalina or Gymnanthemum amygdalinum Delille)

Vernonia amygdalina Delille (VA) grows throughout Africa predominantly in tropical areas, up to a height of about 1–5 m. It is popularly called “bitter leaf” because of its bitter taste. Phytochemical studies of VA revealed the presence of saponine, flavonoids, alkaloids, terpenes, steroids, coumarins, phenolic acids and sesquiterpene lactones [40]. Antioxidant [41] and anti-inflammatory effects have been described [41,42]. Moreover, several reports demonstrated in vivo [43] and in vitro [42] antihyperglycemic effects. A study from Ong et al. (2011) revealed that a VA Ethanolic extract containing 1–5 dicafeoylquinic acid, dicafeoyl-quinic acid, chlorogenic acid and luteolin 7-O-glucoside exhibit antidiabetic effects in streptozotocin-induced diabetic rats [44].

2.3. Blessed thistle (Cnicus benedictus L.)

Cnicus benedictus L. is a wild thistle plant native of the Mediterranean region (from Portugal to France) and also known in other parts of the world including Iran and North America. Leaves, stems, and flowers of blessed thistle were traditionally used as a bitter tonic. It stimulates appetite, enhances bile secretion and possesses hepatoprotective virtue [45]. Studies showed the antioxidant properties of Blessed thistle [46]. Folk medicine reported a possible beneficial effect
in diabetes. However, no scientific report seems to prove this potential so far.

2.4. Burdock (Arctium lappa L.)

Burdock is a perennial herb cultivated as a vegetable. It is native of the old world and was introduced in several countries. Burdock is widely used in popular medicine for hypertension, gout, hepatitis and other inflammatory disorders. Studies showed that Burdock contains many polyphenols among which, several caffeoylquinic acid derivatives such as chlorogenic acid. An extract of Burdock root revealed an increase in glucose uptake in muscular L6 cells pointing out an insulin-sensitizing effect [47]. Antioxidant activity of leaves fractions and anti-inflammatory effects were also reported [48,49]. In streptozotocin-diabetic rats, an ethanolic extract of Burdock root showed antidiabetic effect [50].

2.5. Chamomile (Chamomilla recutita L. or Chamaemelum nobile L.)

There are different species of chamomile represented by the two common varieties: German chamomile (Chamomilla recutita) and Roman chamomile (Chamaemelum nobile). Chamomile is an age medicinal herb, native from many European countries and the Mediterranean region. Traditionally it was used for popular remedies to manage asthma or colic complaints. Chamomile contains many terpenoids and flavonoids contributing to its medicinal advantages. It is an interesting source of antioxidative phenolic compounds, such as apigenin and quercetin [51], and possesses anti-inflammatory activity [52]. Moreover, antidiabetic effects of chamomile flowers extract in obese mice have been demonstrated. In this model, chronic treatment with chamomile extract reduced insulin resistance, glucose intolerance and hyperlipidemia [53].

2.6. Chicory (Cichorium intybus L.)

Chicory is an indigenous vegetable in Europe and America. This plant has been considered a wealth of health benefits including the ability to ease digestive problems, to detoxify liver and gallbladder. Chicory is a natural plant is known to improve oxidative stress and to possess anti-inflammatory properties [54,55]. Moreover, a hydroethanolic root extract rich in caffeoyl derivatives particularly in chlorogenic acid (dicaffeoyl-tartaric acid) (64.2%), and to a lesser proportion in chlorogenic acid (19.6%), was reported to improve (i) insulin-sensitizing effects in vitro on L6 muscular cells and (ii) glucose tolerance in vivo in normal rats, thereby also proving an antihyperglycemic action [27]. The antidiabetic effect was also incorporated in streptozotocin-induced diabetic rats [56,57].

2.7. Dandelion (Taraxacum officinale L.)

Dandelion is an Asian, European and North American herb. It has been used in folk medicine from the treatment of various disorders such as liver disease, gallbladder, and digestive complaints. Dandelion root and leaf have been described to possess hypolipidemic and antioxidative effects on cholesterol-fed rabbits [58]. Anti-Inflammatory activity was also reported [59]. In vitro, antidiabetic effects were described involving alpha-amylase and glucoside inhibition [60], in agreement with results obtained in diabetic patients [61]. In addition, Dandelion is extensively used as a diuretic [62].

2.8. Elecampane (Inula helenium L.)

Elecampane is of Asiatic origin but grows in Europa and America for a long time now. The roots of the plant were traditionally used to treat lung complaints and as a diuretic. Recent in vitro experiments reported antioxidant and antimicrobial activities [63]. Other study showed that ethanol extract of Inula helenium L. reduces inflammatory not only in vitro but also in vivo in septic mice [64]. Elecampane helps stimulate the digestive system because of its slightly bitter qualities. An anti-hyperglycemic virtue has been reported [65].

2.9. everlasting flower (Helichrysum italicum (mill.) Roth)

Helichrysum italicum is a plant from Mediterranean countries. For a long time, it was traditionally used to act against several disorders such as allergies, colds, skin, liver and gallbladder damages or infection [66]. As for its potential interest to prevent or attenuate METS, Helichrysum italicum can inhibit carbohydrate digestion and absorption improving postprandial glucose levels and hyperinsulinemia in experiments performed in rats [67]. In addition, this Asteraceae is known to have anti-inflammatory and antioxidant properties [68].

2.10. False dandelion (Hypochaeris radicata L.)

This plant is native from Europe but has also been introduced in America, Japan, Australia and New Zealand where it can be an invasive weed. All botanical parts of the False dandelion are edible. The leaves and roots are those most often harvested. In horses, its excessive consumption can cause severe tremors [69,70]. Hypeochaeris radicata was used for the treatment of jaundice, rheumatism and antibacterial, antifungal properties with antioxidant and anti-inflammatory activities [71]. To the best of our knowledge, no antidiabetic effect has been described so far.

2.11. Hemp-agrimony (Eupatorium cannabinum L.)

The genus Eupatorium is described to contain several species. It is a decorative plant common on the river banks, side of ditches, at the base of cliffs on the seashores. This plant is indigenous of the middle and northern Europe, temperate Asia and northern America. In Europe one of more known is Hemp-agrimony. Agrimony was traditionally used to treat many diseases like diarrhea, hepatitis and as a detoxifying agent [72]. About its possible applications in METS, agrimony was incorporated in the diet of streptozotocin-diabetic mice, reporting anti-hyperglycemic, insulin-releasing and insulin-like activities [73]. Its antioxidant property related to polyphenolic profile is known. In agreement, Agrimonia eupatoria consumption in healthy subject interferes with a marker of inflammation, oxidative status and lipid metabolism [74]. However, agrimony contains some pyrrolizidine alkaloid-tumorigenic compounds [75]. To the best of our knowledge, no study specifically addressed the issue of Agrimony consumption safety.

2.12. Lettuces/Brickly lettuces (Lactuca serriola L.; Lactuca sativa L.)

These Asteraceae are native of Himalaya, Siberia and Atlantic areas but also cultivated in temperate lands of Europe, India, Pakistan and Iran [76]. These plants are used in traditional medicine as sedative, cough suppressant, anti-septic or gastrointestinal disorders reliever. Their antioxidant and anti-inflammatory activities are known [76–78]. More recently a study on alloxan-induced male diabetic rats revealed antidiabetic effects of aqueous prickly lettuce (Lactuca scariola leaf) extracts [79].

2.13. Milk thistle (Silybum marianum L. Gaern)

Milk thistle is a native of the Mediterranean region of Europa, North Africa and introduced in other continents, including North America. This plant has been used for its health benefits on the liver [80]. An extract of this plant, Silymarin, is known to have antioxidative activity and an anti-inflammatory effect through reduction of TNFα level [81]. The presence of flowers-lignans (Silibinin A) in Milk thistle was reported (i) as a potent agent against insulin resistance and (ii) to reduce diabetic hyperglycemia. Moreover, Silibinin A, isofom 3, has been
demonstrated to possess partial PPARγ agonist effects [82].

2.14. Mouse-ear hawkweed (Hieracium pilosella L.)

Centuries ago Hieracium pilosella was used in traditional herbal treatments. It is native from Europe and Northern Asia, and now can be found as an introduced species in North America, Canada, and New Zealand. Hieracium pilosella has antimicrobial properties and is a potent diuretic plant [83]. Its traditional use targeted bronchitis or bronchial asthma [84]. This plant is also known for its antioxidative and anti-inflammatory activities [83–85]. To the best of our knowledge, no antidiabetic or insulin-sensitizing effect has been reported so far.

2.15. Purple coneflowers (Echinacea purpurea L. Moench)

Echinacea purpurea is one of the most used plant in herbal remedies to prevent and treat many affections such as respiratory tract infections, pain and stomach cramps. It is native of eastern North America and present in the United States and Canada. Among its active constituents, alkaloides, caffeic derivatives and polysaccharides seem to contribute to the immune modulator, antiviral, antioxidant and anti-inflammatory activities of the plant [86]. Moreover, extracts from flowers of Echinacea purpurea have been found able to activate PPARγ (nuclear receptor) and to increase insulin-stimulated glucose uptake in 3 T3-L1 adipocytes. The authors suggest that flowers of Echinacea purpurea contain compounds with the potential to manage insulin resistance and type 2 diabetes [87]. Interestingly chicoric acid found in Echinacea purpurea reverses insulin resistance and suppresses inflammatory responses in the glucosamine-induced HepG2 cells [88].

2.16. Sagebrush (Artemisia herba-alba)

Artemisia herba-alba is an aromatic plant naturally growing in mountain habitats of North Africa (Algeria, Morocco, Tunisia). The sagebrush aerial part is widely used in the traditional medicine to treat bronchitis, diarehas, hypertension and diabetes [89,90]. Hypoglycemic activity of Artemisia herba-alba (Assoc) has been confirmed by in vitro and in vivo experiments with an ethyl alcohol extract [90,91]. Antioxidant activity from aqueous extracts has been reported [91,92]. Moreover, Artemisia decoctions in rats could constitute an excellent adjuvant to manage obesity, hyperglycemia, hypertriglyceridemia, hypercholesterolemia and particularly oxidative stress [93].

2.17. Tarragon (Artemisia dracunculus L.)

Tarragon has its origin in Russia and Mongolia. This Asteraceae is present in European and American countries. Tarragon has been used since ancient times in traditional medicines, having different properties of potential interest for METS. Tarragon, especially the Turkish variety, has antioxidant properties [94] and anti-inflammatory effects [95]. Studies in murine and human muscle cells cultures demonstrated that the antihyperglycemic effect of Russian Tarragon extract are mediated through the insulin signaling pathway [96]. Insulin sensitivity was increased by Russian Tarragon administration [97]. Artemisia dracunculus is included as a plant-derived therapies against METS [98].

Table 1
Antioxidant/anti-inflammatory capacity and insulin-sensitizing/anti-hyperglycemic effects of the major known bitter Asteraceae.

| Common names Asteraceae species | Insulin sensitizing | Anti-hyperglycemic (Antidiabetic) | Anti-inflammatory | Antioxidant |
|--------------------------------|---------------------|-----------------------------------|------------------|------------|
| Artichoke Cynara scolymus      | ✓ (39)              | ✓ (38)                             | ✓ (36,37)        |            |
| Bitter Leaf Vernonia amygdalina | ✓ (43)              | ✓ (40,42)                          | ✓ (41)           |            |
| Blessed thistle Cnicus benedictus | ✓ (47)               | ✓ (50)                             |                 |            |
| Burdock Artemisia lappa        | ✓ (53)              | ✓ (52)                             |                 |            |
| Chamomile Chamomilla reticula  | ✓ (27)              | ✓ (27,56,57)                       | ✓ (54,55)        |            |
| Dandelion Taraxacum officinale | ✓ (60,61)           | ✓ (59,62)                          | ✓ (58,62)        |            |
| Elecampane Inula helenium      | ✓ (65)              | ✓ (64)                             |                 |            |
| Everlasting flower Helichrysum italicum | ✓ (67)    | ✓ (66,67)                         |                 |            |
| False dandelion Hypochaeris radicata | ✓ (68)         |                                     |                 |            |
| Hemp agrimony Eupatorium cannabinum | ✓ (71)         | ✓ (71)                             | ✓ (72)           |            |
| Lettuces Lactuca serriola      | ✓ (77)              | ✓ (74,75,76)                       | ✓ (74,75,76)     |            |
| Milk thistle Silyum marianum   | ✓ (80)              | ✓ (79)                             |                 |            |
| Mouse-ear hawkweed Hieracium pilosella | ✓ (80) | ✓ (82)                            | ✓ (82,83)        |            |
| Purple coneflower Echinacea purpurea | ✓ (85) | ✓ (84)                            |                 |            |
| Sagebrush Artemisia herba-alba | ✓ (88,89)           | ✓ (89,90)                          |                 |            |
| Tarragon Artemisia dracunculus | ✓ (95)              | ✓ (94)                             | ✓ (93)           |            |
| Wormwood Artemisia absinthium  | ✓ (98)              | ✓ (97)                             |                 |            |
2.18. Wormwood (Artemisia absinthium L.)

Artemisia absinthium is native of temperate regions of Eurasia, Northern Africa and naturalized in Canada and the northern United States. It is used as an ingredient in some alcoholic drinks. Its medicinal effects include antimicrobial, antifungal, neuroprotective, hepatoprotective but also antioxidant and anti-inflammatory [99]. Curcumin D (sesquiterpene dimer) is proposed as a significant anti-inflammatory component. Moreover, an antidiabetic effect of Artemisia absinthium extracts on alloxan-induced diabetic rats was reported. The presence of Thujone (monoterpene) in large proportions could participate to their insulin-sensitizing action [100].

Table 1 summarizes our investigations. Most of these bitter Asteraceae possess high potential combination of beneficial properties to prevent or attenuate METS through actions against oxidative stress and insulin resistance.

3. Secondary metabolites from bitter Asteraceae

3.1. Beneficial actions of the sesquiterpene lactones

Numerous plants produce sesquiterpene lactones but seemingly not in the proportions found in the bitter Asteraceae family [101]. The beneficial health effects of sesquiterpene lactones seem to be of potentially major interest especially their anti-inflammatory effect, and reported gastric cytoprotective properties [101,102]. Hyperglycemia is responsible for an inflammatory status through the activation of NF-κB signaling, which is involved in the synthesis of cytokines such as TNFα [103,104]. The suppressive action of sesquiterpene lactones on the degradation of the IκB (inhibitor of NF-κB) reduces the activation of glucose-stimulated NF-κB [105]. It was reported that a chicory root (Cichorium Intybus) extracts rich in sesquiterpene lactones reduced in vivo experiments on rats with a down-regulated expression of the COX2, tnf-α, Il 1b and Inos genes [106].

3.2. The caffeoyl derivatives and their anti-METS effects

The caffeoyl derivatives are C6-C3 phenolic compounds of the hydroxycinnamic acid family. The hydroxycinnamic acids are characterized by the presence of at least one aromatic ring, with one or more attached hydroxyl groups (Fig. 2). Among the hydroxycinnamic acids, most often found in plants are caffeic acid, ferulic acid, chlorogenic acid and chicoric acid. Table 2 shows the caffeoyl derivatives in the bitter Asteraceae cited [47,108-127]. Caffeic acid (CA) and its main derivatives, in particular caffeic acid phenethyl ester (CAPE), are widely produced in fruits, vegetables, coffee and Asteraceae species [107,108]. CA is often under conjugative forms in these plants as caffeoylquinic derivatives (CQAs) comprising the mono- and di-caffeoylquinic forms [18,20]. The chemical analysis of all the caffeoyl derivatives contained in bitter Asteraceae plants is ongoing.

Chlorogenic acid (CGA; before the IUPC nomenclature), which is today called 5-O-caffeoylquinic acid (IUPC nomenclature), and its isomers like 3-O-caffeoylquinic [128] are the most representative members of the mono-caffeoylquinic acids found in abundance in Asteraceae
Table 2
Presence of hydroxycinnamic acids in some bitter Asteraceae species, including caffeic, ferulic, chlorogenic and chicoric acid.

| Common names | Asteraceae species          | Caffeic acid | Ferulic acid | Chlorogenic acid | Chicoric acid |
|--------------|----------------------------|-------------|--------------|-----------------|--------------|
| Artichoke    | Cynara Scolymus             | ✓ (108)     | ✓ (108)      | ✓ (108, 109)    |              |
| Bitter Leaf  | Veronica amygdalina         | ✓ (108)     | ✓ (108)      |                 | ✓ (110)      |
| Blessed thistle | Cnicus benedictus       | ✓ (108)     | ✓ (108)      |                 |              |
| Burdock      | Arctium lappa               | ✓ (47)      | ✓ (47)       | ✓ (47)          |              |
| Chamomile    | Chamaemelum nobile          | ✓ (111, 112)|              |                 |              |
| Chicory      | Cichorium intybus           | ✓ (108)     | ✓ (108)      | ✓ (108)         | ✓ (108, 109, 113, 114) |
| Dandelion    | Taraxacum officinale        | ✓ (115)     | ✓ (115)      | ✓ (115)         | ✓ (114, 114) |
| Elecampane   | Inula helenium              | ✓ (116)     | ✓ (116)      | ✓ (116)         |              |
| Everlasting flower | Helichrysum italicum  | ✓ (118)     | ✓ (118)      | ✓ (117, 118)    | ✓ (114)      |
| False dandelion | Hypochaeris radicata    | ✓ (119)     |              |                 | ✓ (119)      |
| Hemp agrimony | Eupatorium cannabinum      | ✓ (108)     | ✓ (108)      | ✓ (108)         | ✓ (108, 114) |
| Lettuce      | Lactuca serriola            | ✓ (120)     | ✓ (120)      | ✓ (120)         |              |
| Milk thistle | Silybum marianum            | ✓ (121)     |              |                 |              |
| Mouse-ear hawkweed | Hieracium pilosella     |              |              |                 |              |
| Purple coneflower | Echinacea purpurea    | ✓ (122)     | ✓ (122)      | ✓ (122)         | ✓ (114)      |
| Sagebrush    | Artemisia herba-alba        | ✓ (123)     |              |                 | ✓ (124)      |
| Tarragon     | Artemisia dracunculus       | ✓ (108)     | ✓ (108)      | ✓ (108, 125)    |              |
| Wormwood     | Artemisia absinthium        | ✓ (126)     | ✓ (126)      | ✓ (126, 127)    |              |

Fig. 3. Anti-METS actions of the four major hydroxycinnamic acid derivatives. An overnutrition and/or genetic predispositions provokes an oxidative stress of the adipose tissue leading to a chronic inflammation status. Adipose tissue dysfunction and chronic inflammation an insulin resistance. The red arrows indicate the effects of the caffeoyl derivatives. The beneficial action of the caffeoyl derivatives against oxidative stress increase the activities of cellular superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) in adipose tissue. Otherwise, caffeoyl derivatives have a insulin-sensitizing effect by increasing the GLUT4 translocation. CA = caffeic acid, FA = ferulic acid, CRA = chicoric acid, CGA = chlorogenic acid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
like burdock (Arctium lappa) and artichoke (Cynara scolymus) [108].

Chicoric acid (CRA) or dicafeoyltartaric acid (2,3-dicafeoyl-tartaric acid) is present in a few Asteraceae. Among them, chicory (Cichorium intybus) and purple coneflower (Echinacea purpurea) possess a particularly high level of CRA, as do escarole (Cichorium endivia), dandelion (Taraxacum officinale) and lettuce (Lactuca sativa) [114]. Ferulic acid (FA) is widely present in bitter Asteraceae and exhibits antioxidant and anti-inflammatory properties. Combined treatment with FA and CA has been described as protecting against METS in C47 mice [129].

Moreover, caffeic acid and the major derivatives (FA, CGA and CRA) have significant medicinal benefits due to their cardio- and hepatoprotective, anti-hyperglycemic, antioxidant, and anti-inflammatory effects [29]. CA has been used in vivo experiments on db/db diabetic mice showing an anti-hyperglycemic capacity [26]. Ferulic acid may act as an antidiabetic compound by modulating insulin-signaling molecules in the liver [130]. For CGA and CRA, anti-hyperglycemic and anti-diabetic effects have been described [14,113,131].

On Fig. 3, we point out the four major caffeoyl derivatives cellular targets able to slowdown the progression of the metabolic syndrome. The antioxidant action of caffeoyl derivatives is primarily due to their hydroxyl groups, which are easily oxidized due to low bond dissociation energies and which act as ROS scavengers [132,133]. The caffeoyl derivatives have also the capacity to induce cell molecular responses to prevent oxidative stress damage. The major caffeoyl derivatives from bitter Asteraceae, except ferulic acid, enhance enzyme activities and/or gene expression of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) [134–137].

Hydroxycinnamic acids can also act as anti-inflammatory agents on diverse targets. Interestingly, in vivo models of chronic inflammation have revealed that CA, CAPE, CGA and CRA can decrease pro-inflammatory factors such as cytokines (IL-1β, IL6 and TNFα) and NF-κB transcription factor [138–141]. More recently, CA was described as an activator of the PPARγ synthesis pathway [142]. PPARγ is known as an anti-inflammatory molecular target that can reduce the program of NFκB-dependent gene expression in macrophages and inhibit cytokine production [142,143].

In vitro experiments have shown that the major CA, CGA and CRA, but not FA, are able to increase the glucose uptake of adipose and muscular tissues [27,144,145] and consequently reduce insulin resistance.

It was reported that CGA also exhibit an anti-hyperglycemic effect by reducing hepatic glycoenolysis by a reduction of the hepatic glucose 6-phosphatase activity (G6Pase) [146]. Later it was shown that CA and FA have also this inhibitory activity towards G6Pase activity [27]. Another action of CA is the activation of AMP-kinase, leading to an inhibition of hepatic glucose production and fatty acid synthesis [147].

Thus, the four caffeoyl derivatives have rather similar actions, probably due to their structures similarities. However, a recently published study demonstrated the beneficial effect of the association of CRA and CGA on glucose tolerance, with an insulin-sensitizing action. Indeed, a rich caffeoyl derivative extract from chicory root (NCRAE) containing 64.2% CRA and 19.6% CQAs was able to reduce basal hyperglycemia and improve glucose tolerance in streptozotocin (STZ)-containing 64.2% CRA and 19.6% CQAs was able to reduce basal hyperglycemia and improve glucose tolerance in streptozotocin (STZ)-containing diabetic rats. This last beneficial effect was also obtained with a combination of CRA (70%) and CGA (30%), triggering a similar anti-hyperglycemic effect in STZ-induced diabetic rats [113].

An interesting study reported the allosteric inhibition of protein phosphatase B1 (PPTP1B) by both chlorogenic acid and choric acid [148]. PTP1B acts as a major negative regulator of both insulin and leptin signaling, the dysfunction of which is commonly associated in disease states such as diabetes and obesity [149,150] and accordingly METS. Therefore, the combined presence of chlorogenic acid and choric acid in plants seems important to prevent or treat the progression of METS. In agreement, another report underlined the importance of the combination of these two acids among the bioactive components of dandelion (Taraxacum officinale L.), particularly for its anti-diabetic properties [151].

4. Comments

Metabolic syndrome leads to insulin resistance and potentially the development of diabetes via obesity, inflammation and oxidative stress. The 18 bitter Asteraceae that we reviewed in our study demonstrate several pharmacological properties related to an anti-METS action, as well as anti-inflammatory, antioxidant and insulin-sensitizing effects. These were correlated to the chemical data describing the content in caffeic acid and its derivatives in each plant. The information highlighted a significant correlation between the hydroxycinnamic acid derivatives present in Asteraceae and their anti-METS potential. Moreover, the anti-diabetic effects found for most of them seem to corroborate this observation. Recent studies show a benefit on anti-METS activity when caffeoyl derivatives are used in a mixture. The anti-inflammatory beneficial effect of sesquiterpene lactones can act in parallel to hydroxycinnamic acids and derivatives. In conclusion, a diet supplemented with edible bitter Asteraceae species and their associated bioactive compounds seems to be a good alternative to promote a healthy lifestyle, that delays the progression of METS.

Declaration of Competing Interest

None.

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References

[1] K.G. Alberti, P. Zimmet, J. Shaw, Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation, Diabet. Med. 23 (5) (2006) 469–480.
[2] J.A. Kaur, Comprehensive review on metabolic syndrome, Cardiol. Res. Pract. 2014 (2014) (21 pages).
[3] M. Aguilar, T. Bhuket, S. Torres, B. Liu, R.J. Wong, Prevalence of the metabolic syndrome in the United States, 2003-2012, JAMA. 313 (19) (2015) 1973–1974.
[4] G.M. Reaven, Role of insulin resistance in human disease (syndrome X): an expanded definition, Annu. Rev. Med. 44 (1993) 121–131.
[5] L. Chen, R. Chen, H. Wang, F. Liang, Mechanisms linking inflammation to insulin resistance, Int. J. Endocrinol. 2015 (2015) 508409 (9 pages).
[6] S.E. Shoelson, L. Herrero, A. Naaz, Obesity, inflammation, and insulin resistance, Gastroenterology. 132 (6) (2007) 2169–2180.
[7] M.A. McDermot, O.M. Finchane, R.M. Connaughton, A.M. McMorrow, H.M. Roche, Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies, Front Endocrinol (Lausanne). 52 (2013) 1–23.
[8] J.P. Bastard, M. Maaschi, C. Lagathu, M.J. Kim, M. Caron, H. Vidal, J. Capeau, B. Feve, Recent advances in the relationship between obesity, inflammation, and insulin resistance, Eur. Cytokine Netw. 17 (2006) 4–12.
[9] S. Furukawa, T. Fujita, M. Shimabukuro, M. Iwaki, Y. Yamada, Y. Nakajima, O. Nakayama, M. Makishima, M. Matsuura, I. Shimomura, Increased oxidative stress in obesity and its impact on metabolic syndrome, J. Clin. Invest. 114 (12) (2004) 1752–1761.
[10] A. Whaley-Connell, P.A. McCullough, J.R. Sowers, The role of oxidative stress in the metabolic syndrome, Rev. Cardiovasc. Med. 12 (1) (2011) 21–29.
[11] A.N. Fabricatore, T.A. Wadden, Treatment of obesity: an overview, Clinical Diabetes. 21 (2003) 67–72.
[12] M.N. Beidokhti, A.K. Jäger, Review of antidiabetic fruits, vegetables, beverages, oils and spices commonly consumed in the diet, J. Ethnopharmacol. 201 (2017) 26–41.
[13] B. Raspinaz, G. Eskici, A.O. Ocekk, How coffee affects metabolic syndrome and its components, Food Funct. 8 (6) (2017) 2089–2101.
[14] S. Meng, J. Cao, Q. Feng, J. Peng, Y. Hu, Roles of cholecalciferol acid on regulating glucose and lipids metabolism: a review, Evid Based Complement Altern Med. 2013 (2013) (11 pages).
[15] Y. Rochlan, N.V. Pothineni, S. Kovelamudi, J.L. Mehta, Metabolic syndrome: pathophysiology, management, and modulation by natural compounds, Ther. Adv. Cardiovasc. Dis. 31 (8) (2017) 215–225.
[16] E.P. Cherniack, Polyphenols: planting the seeds of treatment for the metabolic syndrome, Nutr. Rev. 70 (12) (2012) 768–776.
S.S. Grecco, C.L. Lancellotti, P. Romoff, J.H. Lago, A.C. Bianco, M.O. Ribeiro, Combinated treatment with caffeic and ferulic acid rom Baccharis uncinella C. DC. (Asteraceae) protect against metabolic syndrome in mice, Braz J Med Res 49 (3) (2016) (7 pages).

A. Narasimhan, M. Chinnaiyan, B. Karunadevi, Ferulic acid exerts its antidiabetic effect by modulating insulin-signalling molecules in the liver of high-fat diet and fructose-induced type-2 diabetic adult male rat, Appl Physiol Nutr Metab. 40 (8) (2015) 769–781.

L.M. Casanova, D. da Silva, M. Sola-Penna, L.M. Camargo, M. Celestrini, L.W. Tinoco, S.S. Costa, Identification of chicoric acid as a hypoglycemic agent from Ocimum gratissimum leaf extract in a biomonitoring in vivo study, Fitoterapia 93 (2014) 132–141.

E. De Oliveira Silva, R. Batista, Ferulic acid and naturally occurring compounds bearing a Feruloyl moiety: a review on their structures, occurrence, and potential health benefits, Compr. Rev. Food Sci. Food Saf. 16 (2017) 580–616.

C.A. Rice Evans, N.J. Miller, G. Paganga, Structure-antioxidant activity relationships of flavonoids and phenolic acids, Free Radical Bio. Med. 20 (1996) 933–956.

A. Schlenzitzauer, C. Oiry, R. Hamad, S. Galas, F. Cortade, B. Chabi, F. Casas, L. Pesevmesse, G. Fouret, C. Coudray, G. Cros, G. Cabello, R. Magoua, C. Cabello, Chicoric acid is an antioxidant molecule that stimulates AMP kinase pathway in L6 myotubes and extends lifespan in Caenorhabditis elegans, PLoS ONE 8 (2013) (11 pages).

E.T. Olayinka, O.S. Ola, A. Ore, O.A. Adeyemo, Ameliorative effect of caffeic acid on caperactistine-Induced hepatic and renal dysfunction: Involvement of the anti-oxidant defence System, Medicines (Basel) 4 (4) (2017) (13 pages).

R.H. Yilmaz, E. Uz, N. Yucel, I. Altuntas, N. Ozcelik, Protective effects of chlorogenic acid on lipid peroxidation and antioxidant enzymes in diabetic rat liver, J. Biochem. Mol. Toxicol. 18 (4) (2004) 234–238.

Y. Xi, W. Jiao, J. Cao, W. Jiang, Effects of chlorogenic acid on capacity of free radicals scavenging and proteomic changes in postharvest fruit of nectarine, PLoS ONE 12 (8) (2017) (14 pages).

M. Zhang, J. Zhou, L. Wang, B. Li, J. Guo, X. Guan, Q. Han, H. Zhang, Caffeic acid reduces cutaneous tumor necrosis factor alpha (TNF-α), IL-6 and IL-1β levels and ameliorates skin Edema in acute and chronic model of cutaneous inflammation in mice, Biol. Pharm. Bull. 37 (3) (2014) 347–354.

S.J. Hwang, Y.M. Kim, Y. Park, H.J. Lee, K.W. Kim, Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells, Inflamm. Res. 63 (1) (2014) 81–90.

R.M. Bezerra, L.F. Veiga, A.C. Caetano, P.L. Rosalen, M.E. Amaral, A.C. Palanch, S.M. de Alencar, Caffeic acid phenethyl ester reduces the activation of the nuclear factor xB pathway by high-fat diet-induced obesity in mice, Metab. Clin. Exp. 61 (11) (2012) 1606–1614.

Q. Liu, Y. Chen, C. Shen, Y. Xiao, Y. Wang, Z. Liu, X. Liu, Chicoric acid supplement prevents systemic inflammation-induced memory impairment and amyloidoigenesis via inhibition of NF-κB, FASEB J. 31 (4) (2017) 1494–1507.

V. Bermúdez, F. Finol, N. Parra, M. Parra, A. Pérez, L. Peñaranda, D. Vilchez, J. Rojas, N. Arráz, M. Velasco, PPAR-gamma agonists and their role in type 2 diabetes mellitus management, Am. J. Ther. 17 (3) (2010) 274–283.

H.S. Kim, Y.C. Hwang, S.H. Koo, K.S. Park, M.S. Lee, K.M. Kim, M.K. Lee, PPAR-γ activation increases insulin secretion through the up-regulation of the free fatty acid receptor GPR40 in pancreatic ß-cells, PLoS ONE 8 (1) (2013) (12 pages).

E.S. Lee, K.O. Uhm, Y.M. Lee, M. Han, M. Lee, J.M. Park, P.G. Suh, S.H. Park, H.S. Kim, CAPE (caffeic acid phenethyl ester) stimulates glucose uptake through AMPK (AMP-activated protein kinase) activation in skeletal muscle cells, Biochem. Biophys. Res. Commun. 361 (4) (2007) 854–858.

D. Tousch, A.D. Lajoix, E. Hous, J. Azay-Milhau, K. Ferrare, C. Jahnauant, G. Gros, P. Petit, Chicoric acid, a new compound able to enhance insulin release and glucose uptake, Biochem. Biophys. Res. Commun. 377 (1) (2008) 131–135.

H. Hemmerle, H.J. Burger, P. Below, G. Schubert, R. Rippel, P.W. Schindler, E. Paulus, A.W. Herling, Chlorogenic acid and synthetic chlorogenic acid derivatives: novel 531 inhibitors of hepatic glucose-6-phosphate translocase, J. Med. Chem. 40 (1997) 137–145.

K.W. Ong, A. Hsu, B.K. Tan, Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation, Biochem. Pharmacol. 85 (9) (2013) 1341–1351.

S.K. Baskaran, N. Goswami, S. Selvaraj, V.S. Muthusamy, B.S. Lakshmi, Molecular dynamics approach to probe the allosteric inhibition of PTP1B by chlorogenic and cichoric acid, J. Chem. Inf. Model. 52 (8) (2012) 2004–2012.

K.A. Kenner, E. Anyanwu, J.M. Olefsky, J.J. Kusari, Protein-tyrosine phosphatase-1B is a negative regulator of insulin- and insulin-like growth factor-I-stimulated signaling, Biol. Chem. 271 (33) (1996) 19810–19816.

S. Koren, I.G. Fantus, Inhibition of the protein tyrosine phosphatase PTP1B: potentional therapy for obesity, insulin resistance and type-2 diabetes mellitus, Best Pract. Res. Clin. Endocrinol. Metab. 21 (4) (2007) 621–640.

F.E. Wirngo, M.N. Lambert, P.B. Jeppesen, The physiological effects of dandelion (Taraxacum Officinale) in type 2 diabetes, Rev. Diabet. Stud. 13 (2–3) (2016) 113–131.