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POTENTIAL NATURAL IRON CHELATING COMPOUNDS FROM PLANTS

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ABSTRACT

Accumulation of iron in the body results in initiation and propagation of reactive oxygen species, which start to attack the cell vital macromolecules such as proteins, lipids, RNA and DNA causing cell damage, DNA mutation and ultimately cell death. Iron overload is implicated in many disorders in the body such as heart failure, liver cirrhosis and fibrosis, gallbladder disorders, diabetes, arthritis, depression, infertility, and cancer. Even though synthetic chelating agents are available, they have several limitations such as poor oral bioavailability, short plasma half-life, high cost and several side effects. Several researchers have been interested in studying iron overload problems in the body for finding an efficient and natural iron chelators with high safety margin and economic cost from different sources to replace synthetic drugs which exhibited many of limitations. Plants rich of polyphenolic compounds could act as an antioxidant and natural chelators sources since they have more ability to chelate with iron metal forming soluble, stable complexes that can be excreted in the feces and/or urine thereby preventing damaging effects of iron overload. This is a review on plants and isolated compounds which may have potential iron chelating activity.

KEYWORDS

Iron overload, Hemochromatosis antioxidant activity, Iron Chelation, Flavonoids and Phenols.

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INTRODUCTION

Hemochromatosis (iron overload) is the state of accumulation iron in the body into toxic level, it is caused by genetic disorder of protein involved in regulation of iron absorption or due To multiple transfusion of iron in chronic anemia such as sickle cell disease, thalassemia and liver cirrhosis (Queiroz-Andrade *et al.,* 2009)[1]. Accumulation of iron in the body results in initiation and propagation of reactive oxygen species, which start to attack the

cell vital macromolecules such as proteins, lipids, RNA and DNA causing cell damage, DNA mutation and ultimately cell death. This produced state of oxidative stress is associated with many health problems such as heart failure, liver cirrhosis, fibrosis, gallbladder disorders, diabetes, arthritis, in fertility, and cancer (Gupta, 2014)[2]. About 71% mortality are recorded in beta thalassemia patientswhosuffer from cardiac diseases due to accumulation of iron in myocardium (Mobarra *et al.,* 2016)[3]. Several researchers have been interested in studying iron overload problems in the body for finding an efficient and natural iron chelators with high safety margin and economic cost from different sources to replace synthetic drugs which exhibited many of limitations (Mobarra *et al.,* 2016)[3]. Plants rich of polyphenolic compounds could act as an antioxidant and natural chelators sources (Pandey and Rizvi, 2009[4], Symonowicz and Kolanek, 2012)[5] since they have more ability to chelate with iron metal forming soluble, stable complexes that can be excreted in the feces and/or urine thereby preventing damaging effects of iron overload (Ebrahimzadeh *et al.,* 2008)[6]. This is a review on plants and isolated compounds which may have potential iron chelating activity.

Characterizations of Polyphenols compounds

Polyphenols are cyclic derivatives of benzene with one or more hydroxyl groups associated to the aromatic ring (Andjelković *et al.,* 2006)[7] and it is secondary plant metabolites they are abundant in the majority of fruits and vegetables (Brglez Mojzer *et al.,* 2016)[8]. The main classes of polyphenols are phenolicacids, flavonoids, stilbenes and lignans which are recently recognized (Andjelković *et al.,* 2006)[7]. They have highly antioxidant properties more than vitamins they have attracted considerable interest (Brglez Mojzer *et al.,* 2016)[8]. Two mechanisms are commonly proposed to explain the Antioxidant activity these are free radical scavenging and metal chelation which it depends on the number and position of hydroxylgroups bound to the aromatic ring, the binding site and mutual position of hydroxyl groups in the aromatic ring, and the type of substituents, also the metal chelating ability is related to the presence of ortho-dihydroxy polyphenols. if the number of hydroxyl groups in polyphenols is higher the antioxidant capacity and chelation ability is also better (Andjelković *et al.,* 2006[7], Symonowicz and Kolanek, 2012)[5].

Iron chelation assays

Ferrozine reagent

The method was described by (Dinis *et al.,* 1994)[9], in briefly 50 µl of ferrous chloride) to 20 µl of diluted extracts (sample) to 20 µl of methanol (control sample) of and 200 µl of ferrozine (5mM) then1230 µl of methanol were added to bring the final volume of thereaction mixture to 1500 µl After a 10-min incubation the reaction mixture was read at 562 nm against the blank. EDTA was used as positive control. If plant have a strong chelating capacity it will bind with ferrozine therefore inhibit formation ferrozine-iron complex and reduce colour produced (Okoko and Ere, 2012)[10].

2, 2` bipyridyl reagent

the method was described by (Yamaguchi *et al.,* 1999)[11], Briefly, 250 µl of 3 Mm FeSO4, 1 ml of 0.2 M 2`,2-bipyridyl solution,1 ml of 0.2 M Tris-HCl, 400µ 1 of10% hydroxyl amine, 2.5 ml of methanol and 100 µl of distillated water were added to each extract sample (250 µl, 1 mg/ml). The absorbance was determined at λmax 522 nm and used to evaluate Fe2+ chelating activity using ethylenediamine tetra acetate (EDTA) as a standard. Also here the chelation activity of plant is inversely proportional with colour degree resulting from binding reagent and iron (Moss and Mellon, 1942)[12].

Antioxidant assay

Antioxidant Activity Using the ABTS, DPPH, NADH and NO Free Radical Scavenging Methods

Each of ABTS, DPPH, NADH and NO reagents have an unstable radical and used to examine antioxidant capacity of plant sample. The decrease of reagent colour proportional with power of plant as antioxidant agent Lissi *et al.* (1999)[13] (Ak and Gülçin, 2008[14], Yuan *et al.,* 2015)[15].

Examples of herbs with Iron chelating Activity

Green Tea

Green tea (GT) which is produced from the leave of the *Camellia sinensis* plant belongs to the family *Theaceae* (Namita *et al.,* 2012)[16]. It is an excellent source of polyphenolic, particularly Catechins. (GT) catechins such as epicatechin (C) isomers including (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin 3-gallate (ECG), and (-)-epigallocatechin 3-gallate (EGCG). Many of studies have been demonstrated the (GT) catechins act directly as radical scavengers of oxygen and nitrogen species and exert indirect antioxidant effects in addition to possess well-established metal-chelating properties due to a high iron-binding affinity of galloyl group-conjugated in catechins. In previous study on animal model suffer from neurodegeneration disease like Parkinson's and Alzheimer's. The ability of GT polyphenols to act as metal chelators and to have access to the brain makes them a novel promising therapeutic approach for treating neurological diseases. Also (GT) extract showed reduce in plasma non-transferrin band iron level in of thalassemia patient and it has the potential to inhibit ROS generation in iron-treated RBCs and in plasma (Mandel *et al.,* 2006a[17]. Srichairatanakool *et al.,* 2006)[18].

***Psidium guajava* (Guava)**

It is belong to family *Myrtaceae*. The leaves are contained huge amounts polyphenolics including: gallic acid, ferulic acid, catechin, epicatechin, ruin, quercetin, quercetin-3-O-α-L-arabinofuranoside, quercetin-3-O-β-D-arabinopyranoside, quercetin-3-O-β-D-glucoside and quercetin-3-O-β-D-galactoside. On this basis it is demonstrated strong antioxidant properties compare to other parts which attributed to their free radical-scavenging ability of $ABTS^+$ radicals and superoxide anion. Phenolic acid (ferulic acid) may is responsible for Antioxidant capacity. (Chen and Yen, 2007[19], Wang *et al.,* 2014)[20]. In a previous comparating study *Psidium guajava* displayed better iron chelating activity than *Persea Americana* leaves extract by use method stated by (Dinis *et al.,* 1994)[9]. The basic principle is based on the capacity of plant extract to decolourise iron

–Ferrozine complex. Ferrozine is a substance which can quickly acton iron to form colored complex (Kumar *et al.,* 2014)[21].

***Morus alba* (White Mulberry)**

Mulberry is belong to family *Moraceae,* the leaves have potent antioxidant effect which examined by measuring its inhibition effect on LDL oxidation which induce by iron overload result in atherosclerosis (Katsube *et al.,* 2006)[22]. Also by using range of *in vitro* studies the leaves exhibited a strong ABTS radical scavenging, superoxide radical scavenging of $NADH^+$which based on loss colour of $NADH^+$ and Fe2+ chelating power using ferrozine reagent (Yuan *et al.,* 2015)[15]. These activities due to high polyphenols contents such as phenolic acids Gallic, Protocatechuic, phydroxybenzoic, Vanillic, Chlorogenic, Caffeic, p-coumaric Ferulic, Sinapiccaffeoylquinicacid and flavonoids (Quercetin 3-β-D-glucoside, Kaempferol 3-β-D- glu-copyranoside (Flaczyk *et al.,* 2013)[23] as well as rutin (quercetin 3-rutinoside) isoquercitrin (quercetin 3-glucoside) and quercetin 3-(6-malonyl)-glucoside which cited as the major LDL antioxidant components (Katsube *et al.,* 2006)[22]. In addition a previous comparative study with black mulberry (*Morus nigra*) found that the level of phenolic acid was slightly higher in *M.nigra* than *M.alba* even though antioxidant capacity by $DPPH^+$ method was slightly higher in *M.alba*but both showed similar antioxidant capacity by ABTS and also a high content in phenolic compounds and antioxidant activity of mulberry leaves in comparison with mulberry fruits (Sánchez-Salcedo *et al.,* 2015)[24].

***Mangifera indica* (Mango)**

It belongs to family Anacardiaceae. It had a potential anti-oxidant, a powerful scavenging activity of hydroxy radicals and strong chelator of iron in many of *in vitro* studies by using commonly accepted assays (Ling *et al.,* 2009)[25] (Martínez *et al.,* 2000)[26] (Sánchez *et al.,* 2000)[27]. And also it showed a strong anti-oxidant capacity though using some of *in vivo* experiment on rats such as

significant inhibitory effect on the peroxidation of rat brain phospholipid and prevented DNA damage caused by bleomycin or copper-phenenthroline systems (Martínez *et al.,* 2000)[26] the previous activity are attributed to high content of polyphenolic compounds in *M. Indica* (Masibo and He, 2008)[28]. The leaves are rich with is omangiferin, homomangiferin**,** gallic acid, methyl gallate, maclurin 3-*C*- *β*-D-glucoside,3,4-dihydroxybenzoic acid, iriflophenone 3-*C*-*β*-D-glucoside,iriflophenone 3-*C*-(2-*O*-galloyl)-*β*-D-glucoside, iriflophenone 3-*C*-(2-*O*-*p*-hydroxybenzoyl)-*β*-D-glucoside, iriflophenone mono-*O*-galloyl-glucoside, penta-*O*-galloyl-glucoside, iriflophenone 3-*C*-(2,6-di-*O*-galloyl)-*β*-D-glucoside, 6-*O*-(*p*-hydroxybenzoyl) mangiferin, isoquercitrin isomers, quercetin pentosides (Barreto *et al.,* 2008)[29]. (–)-epicatechin-3-*O*-β-glucopyranoside, 5-hydroxy-3-(4-hydroxylphenyl)pyrano[3,2-*g*]chromene-4(8*H*)-one, 6-(*p*-hydroxybenzyl) taxifolin-7-*O*-β-D-glucoside (tricuspid), quercetin-3-*O*-α-glucopyranosyl-(1→2)-β-glucopyranoside, (–)-epicatechin (2-(3, 4-dihydroxyphenyl)-3, 4-dihydro-2*H*-chromene-3, 5, 7-triol) (Kanwal *et al.,* 2009)[30]. Mangiferin are considered the major compound found in mango it is worth to be mentioned that the part of anti-oxidant could be ascribed to mangiferin as a main component (Shah *et al.,* 2010)[31] by its iron-chelating properties not merely due to the scavenging activity of free radicals. The study was conducted on rat liver, where mangiferin showed iron-complexing as a primary mechanism for protection of rat liver mitochondria against Fe^{+2} – citrate induced lipid peroxidation. It also inhibited the iron citrate induction of mitochondrial antimycin A-insensitive oxygen consumption, stimulated oxygen consumption due to Fe2+ autoxidation and prevented Fe3+ ascorbate reduction (Singh *et al.,* 2009)[32].

***Carica papaya* (Papaya)**

It belong to family Caricaceae. The leaves part had the higher phenols contents (Folin-Ciocalteu's reagent), flavonoids contents (aluminium trichloride) and significant higher radical scavenging (DPPH method) when compared to other plant parts in a previous study (Maisarah *et al.,* 2013)[33]. Also they proved to be effective for inhibition erythrocyte haemolysis and peroxidation by radical scavenging capacity of hydrogen peroxide and hydroxyl radical also by iron metal chelating, the oxidation of erythrocyte was good model for oxidation biomolecules in general (Okoko and Ere, 2012)[10] all those activity due to rich contents of polyphenols in papaya leaves, the flavonoid which isolated from leaves are quercetin 3-(2G-rhamnosylrutinoside), kaempferol 3-(2^G-rhamnosylrutinoside), quercetin 3- rutinoside, myricetin 3-rhamnoside, kaempferol 3-rutinoside, quercetin, and kaempferol (Nugroho *et al.,* 2017)[34] and phenolic acid like caffeic acid, *p*-coumaric acid, caffeoyl malate, *p*-coumaroyl malate isomers and feruoyl malate isomers (Afzan *et al.,* 2012)[35].

***Cymbopogon citratus* (Lemon grass)**

It belongs to family Poaceae, Many of a conducted study on L. grass which resulting in a significant scavenging ability of DPPH, ABTS and hydroxyl superoxide. Also a moderate anti-lipid peroxidative effect and concluded that Lemon grass has high antioxidant capacity. The most active principle having antioxidant property are not only vitamins but alsopolyphenols. The main compounds obtained from the plant *C*-glycosyl flavones orientin and iso-orientin as well as chlorogenic acid (Nambiar, 2012)[36]. And it had a strong inhibition effect on lipids peroxidation by use TBA method and it showed a chelation activity of ferrous ion by interfere the formation of ferrozine through in vitro study, Ferrous ions are one of the most effective pro-oxidants; their interaction with hydrogen peroxide in biological systems can lead to formation of highly reactive hydroxyl radicals (Geetha and Geeetha, 2016)[37]. It worth to be mentioned The essential oil of L. grass demonstrated high Anti-oxidant activity by DPPH and scavenging tests (Lawrence *et al.,* 2012)[38] such as β-Myrcene, Geraniol, Geranyl acetate, Geranial, (E)-IsoCitral, Citronellal, *exo-Iso Citral,* (Z)-Iso Citral, Citronellol + Nerol, Oxygenated monoterpenes (Vyshali *et al.,* 2016)[39].

***Vitisvinifera* (Grape)**

It belongs to family Vitaceae. Leave of grape are rich with natural source of polyphenol compounds with good antioxidant effect, such as 3-Hydroxybenzoic acid, Gallic acid, Caffeic acid, Vanillin acid, (+)-Catechin, (-)-Epicatechin, Apigenin, Quercetin, Myricetin, Quercetin-4'-glucoside, Rutin (Katalinić *et al.,* 2009)[40]. Myricetin, ellagic acid, kaempferol (Xia *et al.,* 2010)[41]. Quercetin-3-O-galactoside, quercetin-3-O-glucoside, and quercetin-3-Oglucuronide, cyanidin-3-O-glucoside and peonidin-3-Oglucoside (Dresch *et al.,* 2014)[42]. In a previous comparative study of grape leaves collected in different time of year the result Both extracts showed a significant capability of chelating grape (Katalinić *et al.,* 2009)[40] and another conducted study to compare between different grape fractions the EtOAc Fr. had the highest total phenolic content as well as the highest antioxidant activity when determined by the DPPH and superoxide anion scavenging assays, while CHCl3 Fr. showed the highest antioxidant activity when evaluated by the metal chelating assay (Dresch *et al.,* 2014)[42].

Examples of isolated compounds exhibited chelating and antioxidant activity

Curcumin

Many of studies on curcumin which proven the curcumin had a potential iron chelating activity and potent antioxidant capacity. The study was conducted by treatment iron-overloaded rats with curcumin resulted in marked decreases in iron accumulation within liver and spleen, accordingly inhibition lipid peroxidation and scavenging activity of NO in liver and spleen (Badria *et al.,* 2015)[43].

Quercetin and Rutin

In a previous study of inhibitory effect of these flavonoids on ferrous ion-dependent lipid per oxidation of lecithin liposomes and NADPH-dependent lipid peroxidation in rat liver microsomes, found both flavonoid compounds inhibited lipid peroxidation of lecithinliposomes even at high iron ion concentrations (1 mM). Both flavonoids were significantly more effective inhibitors of iron ion-dependent lipid peroxidation systems due to chelating iron ions with the formation of inert iron complexes unable to initiate lipid peroxidation. At the same time, iron complexes of flavonoids retained their free radical scavenging activities. The effects on NADPH-dependent lipid per oxidation in rat liver microsomes were compared with a classical antioxidant, 3, 5-di-tert-butyl-4-hydroxytoluene (BHT). Quercetin being a more powerful inhibitor. Both are inhibit more strongly the NADP-dependent lipid peroxidation, Thus, the ability of rutin and quercetin to reactwith superoxide ion and lipid peroxide radicals and to form iron complexes which are unable to catalyse the formation of active oxygen radicals (Afanas' ev *et al.,* 1989)[44].

Catechins

They have a potential antioxidant activity as well as strong chelating agent. And they showed ability to penetrate blood brain barrier in brain by using range of *in vitro* and *in vivo* studies, therefore prevent iron-induced oxidative stress and aggregation of alpha-synuclein and beta-amyloid peptides. They couldbe a natural, non-toxic, brain permeable neuroprotective drugs useful with Parkinson's and Alzheimer's diseases pathology (Mandel *et al.,* 2006b)[45].

Kolaviron

It is a natural biflavonoid from *Garsinia kola* seed, was shown protect against oxidation lipoprotein in rats through the chelating activity and it suggesting may have protective effect against atherosclerosis.

Floranol

It is a new flavonoid isolated from roots of *Dioclea grandiflora,* it has ability to chelate with Fe ad Cu, hence prevented formation free radical which oxidize low density *lipoprotein.*

Apocynin

It derived from rhizome *Picrorbiza korroa*, which have ability to cross blood brain barrier and can exert antioxidant and chelating activity in brain (Hatcher *et al.,* 2009)[46].

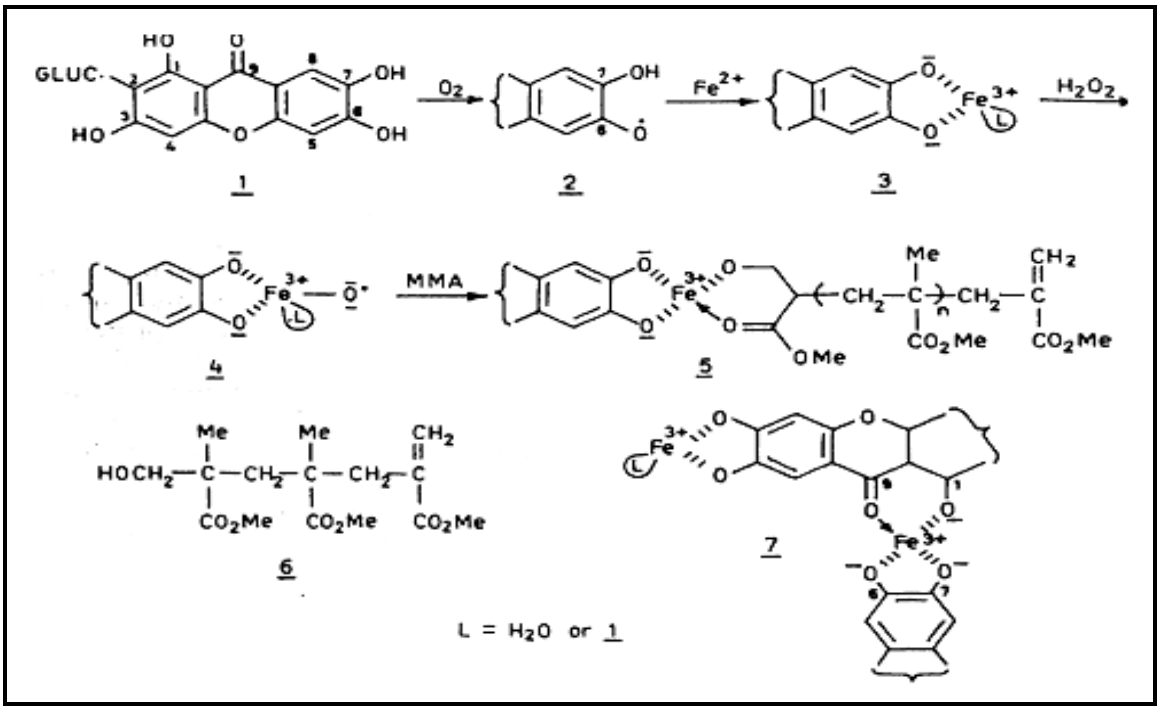

Figure No.1: Mechanism of action of Mangiferin as iron chelator agent (Masibo and He, 2008)[28]

CONCLUSION

In summary, we observed that some of selected plant leaves and isolated compounds which proven to be an effective iron chelating and antioxidant agents. We selected the leaves part since they rich with polyphenol and they easier to collect them and to protect environment from global pollution hazard. Natural sources are offer many of advantages over the synthetic ones, they are economic, increase safety concern and available source. Future strategies are finding the factors which encourage customers to proper consume natural products.

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CONFLICT OF INTEREST

There is no conflict of interest.

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