



Dihydromyricetin, a multi-perspective medicinal entity

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Key words: DHM, Anti-cancer, Anti-oxidant, ROS.

<http://dx.doi.org/10.12692/ijb/14.5.378-388>

Article published on May 26, 2019

Abstract

Dihydromyricetin called flavonoid also known as ampelopsin and extract from *Ampelopsis grossedentata*, it found in various species of plants such as Japanese Raisin Tree, the Himalayan Cedar Tree, the African Blackwood but it mostly obtained from *Ampelopsis grossedentata* which mostly occurs in the warm climate of china. Dihydromyricetin exhibit a lot of biological activities with minimum side effects, it shows anti-cancer, apoptotic, anti-inflammatory and anti-oxidant activity, dihydromyricetin play an important role in anti-inflammation after binding to a novel binding site IKK β -Cys46, it may scrounge the reactive oxygen species and shows oxidative stress mediating activity and also selectively diminish cancer cell without effecting normal cells by this way it have anti-tumour activity. DHM cause the induction of apoptosis by interfering with many signaling pathways such as ERK1/2 and p38 MAPK, Bcl2/Bax, DR4 and DR5, increase activity of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) can cause the elimination of EtOH and by this way DHM amend the liver injuries due to alcohol consumption and so act as a novel anti-alcohol agent. Previous researches makes a lot advances in clinical applications of DHM but this is not enough further researches also need to do. Lower and high levels of dihydromyricetin may limits its potential applications, in this review we will discuss the different biological activities of dihydromyricetin and how it works as a multi-perspective medicinal Entity.

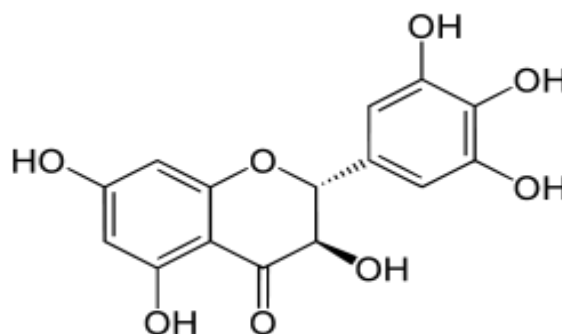
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Introduction

Dihydromyricetin, belonging to flavonoid family, also known as ampelopsin, it is isolated from *Ampelopsis grossedentata*, it occurs extensively in the southern China. Traditionally, Yao people in china used *Ampelopsis grossedentata* as tea, used to treat pyretic fever and cough, pain in pharynx and larynx, and jaundice hepatitis. It is also used in nephritis, hepatitis, halitosis, and polyorexia prevention and treatment, recent studies have proved that dihydromyricetin shows multiple health-benefiting activities, including anti oxidative, anti-inflammatory, anti-tumour, anti-bacterial, apoptotic activity, and lipid and glucose-metabolism-regulatory activities. Approximately 90% of colorectal cancer (CRC) are derived from benign adenomatous lesions, which are estimated to take 5–15 years to evolve into invasive cancer and it is one of the most frequently occurring cancers around the world (Murakami *et al*;2004). Alcohol use disorders (AUD) represent a considerable public health problem worldwide. Over 76 million people present with AUD; 2.5 million deaths were attributed to alcohol. Repeated alcohol use leads to the development of AUD, leading to tolerance, withdrawal syndrome (AWS) including hyper excitability, distress, anxiety, insomnia, agitation, occasional seizures, and dependence. Due to the deficiency of active medications that upgrade AWS and cure alcohol reliance, only 13% of people recognized withAUD have ever received special treatment. Mainly most of the organ systems are effected by the ingestion of alcohol (EtOH), its effects on the brain are of vital importance to AUD, given EtOH's numerous neuro pharmacological actions, including its intoxicating, sedative, anxiolytic, strengthening, and addictive properties (Heilig *et al*;2010). Dihydromyricetin (DMY), it is a flavonoid and extracted from *Ampelopsis grossedentata* also known as ampelopsin, it is ascribed with hepatoprotective properties and also showed antioxidant activity in forwardstudies (Hase *et al*;1997). Dihydromyricetin is the richest component found in *Ampelopsis grossedentata*. According to recent studies its biologically have confirmed that dihydromyricetin exhibit numerous health-benefiting

activities, including antioxidative, anti-inflammatory, anticancer, antimicrobial, cell death mediating, and lipid and glucose-metabolism-regulatory activities. In this review article, these biological activities will be discussed comprehensively.

Chemical Composition of Dihydromyricetin Ampelopsin



IUPAC Name

(2*R*,3*R*)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one.

Other Names

Dihydromyricetin, Ampeloptin,(+)-Ampelopsin,(+)-Dihydromyricetin.

Chemical formula

$C_{15}H_{12}O_8$

Molar mass

$320.25 \text{ g}\cdot\text{mol}^{-1}$

Reticence of incursion and immigration

Main cause of death is metastasis and is directly related with cancer, invasion and metastasis of cancers is directly affected by numerous others factors. The metastatic process of cancer is meaningfully drop by dihydromyricetin by obstructing the humiliation of the basement membrane. *in vitro* experiments, it is confirmed that the devotion of B16 mouse melanoma cells to fibronectin, lamin, or matrigelcan also prevented by dihydromyricetin, thus lessening conquest into the reconstructed basement membrane (Liu *et al*; 2003). Extracellular matrix constituents is capable of digesting by a group of membrane associated protiens called matrix metalloproteinases MMPs , so perform

an important part in cancer spreading. Additionally, the up-regulation of MMP-2/-9 countenance is main acute stage of incursion and spreading of tumor cells. Incursion of human breast cancer cells can inhibited by dihydromyricetin, this comprise down-regulated countenance of MMP-2/-9 in cooperation the extracellular matrix and intracellular space (Chakrabarti *et al*; 2003). Furthermore, the

expression of CXCR4 may inhibited by ampelopsin, Reticence of assault and relocation of prostate cancer cells caused by a protein related with these prostate cancer cells. In clinical cancer treatments Adriamycin (ADM) is used as an important anti-cancer agent. But the use of ADM is restricted due to its cytotoxic effects to skeletal muscles, liver and heart (Zhou *et al*; 2012).

Table 1. Biological Activities Of Dihydromyricetin.

Cell types/animals	Biological Activities
Mesenchymal stem cells	Fundamental foraging↑
Mice	motor dysfunction↓; learning and memory damages↓; MDA↓; glucose uptake↑
Mice Liver	JNK↑; inflammation↓; apoptosis↓; propagation↑
Rats	glucose endorsement↑; GLU1↑; krebs↑; insulin conflict↓;
PC12 cells	Cellular oxidative stress↓; GLUT4 translocation dysfunction ↓; Glo-1 ↑
Cardiac fibroblast	ROS↓; MDA↓; p22phox ↓; SOD↑; thioredoxin↑; total anti-oxidant capacity↑; proliferation↓; collagen synthesis↓
LDLr ^{-/-} mice	atherosclerotic inscriptions↓;IL-6↓; TNF-α ↓; lipoidaemia ↓; foam cell↓; cholesterol effluence↓
HFD-fed mice	IL-6↑; TNF-a↑
Primary HUVECs	ROS↓; p53↓; Bcl-2↑; Bax↓; caspase-3↓; caspase-9↓; lipid amassing↓; ROS↓; NO ₂ ↓
Diabetic F.A	insulin confrontation↓
LPS-induced rat kidney	Nitrogen in blood and urea↓;apoptosis↓

Anticancer activity

Liver cancer is the third most common cause of cancer-related death and is a major malignant tumor worldwide. More than 80% of liver cancer patients are diagnosed with hepatocellular carcinoma (HCC), and resistant to most conventional chemotherapeutic agents. Moreover, the use of chemoprevention agents is usually associated with many side effects which lead to the destruction of normal tissues, such as those of the digestive, hematopoietic and nervous systems (Bonadonna *et al.*, 1969). Dihydromyricetin (DHM), a flavonoid extract isolated from *Ampelopsis grossedentata*, functions as an anti-intoxicant, anti-inflammatory and anti-oxidative agent. Adriamycin (ADR), cytotoxic drugs used in oncology and most commonly recommended and active cytotoxic

remedies which belongs to anthracyclines, and used in order to cure the cancers of numerous kinds and also related with beneficial medical effects, containing numerous myeloma, leukemia, sarcoma, lymphoma and so on. Though, besides that, a severe contrary consequence being life-threatening heart injury furiously restricted its healing prospective. Further researches exhibited that myocardial poisonousness revealed in its utmost fatal form by severe heart arrest (Congestive heart failure ,CHF) and it occurs after the end of the therapy (it takes months to years) or during the Adriamycin treatment and the poisonous wound fundamentally elevated as soon as ADR accumulated in a dose dependent manner. Previous researches have demonstrated that the risk of progress of heart diseases (congestive heart failure) is 26% when the accumulative doses reaches to 550

mg/m², and death rate around 30%-50% around (Swain *et al*; 2003). The severe cardiac intensive care, the use of anthracycline correspondents with minor cardiotoxicity, and alterations of the program of administration these several approaches could be considered in order to diminish ADR associated cardiotoxicity. In the last 40 years after the first exposure of the severe cardiotoxicity triggered by ADR, numerous struggles have done to explore the dynamic methodologies to improve it. Numerous mediators comprising amifostine, phenylbutyrate, and glutathione (Vergely *et al*; 2007), were set up to recover ADR-persuaded cardiotoxicity. On the other hand, there is only one compound *i.e.*, dexrazoxane, introduced by Kurt Hellmann, it has therapeutic properties and used as a cardioprotective agent. Around 90% of CRC are derived from benign adenomatous lesions and is one of the most frequently occurring cancers worldwide, which are probable to take 5–15 years to progress into invasive cancer (Watson, A. J, 2006). One chief impairment to chemotherapy for the treatment of CRC comprises numerous members of the ATP-binding cassette (ABC) superfamily of membrane transporters, in result anti-cancer agents can pump out through the cell membrane and lessen the intracellular drug accumulation. In addition, several errors in pathways controlling apoptosis that arise during the development of CRC generally increase the cancer cells' survival and suppress apoptosis (Minko *et al*; 2004).

Apoptotic activity

Apoptosis is one of the distinctive death ways which is somewhat dissimilar from conventional necrosis. Kerr *et al.* in 1972 was the first who explain this phenomenon, its molecular mechanism was becoming clear until the late 1980s. Cell death is induced by a class of antibody that is IgM and this phenomenon was exposed by Yonehara *et al.* Nagata *et al.* cloned analogous antigen on the surface of cell, which is known by Fas and its physiological ligand is also replicated by them called Fas ligand and this gene belongs to the family of tumor necrosis factor (Suda *et al*; 1993). C. elegans

cell death gene, is discovered by Horvitz *et al.* in 1993, it has notable sequence resemblance to mammalian ICE and it is also answerable for development of pro-IL-1. These proteases possess some distinctive features, so they also known as caspases, and they have a cysteine residue (C) in their active site and slash target molecules C-terminal to aspartate (Asp) residues (Thornberry, Lazebnik; 1998, Wolf, Green; 1999). Apoptosis is a process of programmed cell death, which reveals acute role in cellular physiopathology of various tissues and organs. Dihydromyricetin, down-regulates the expression of p53 and up-regulation Bcl-2 expression in a dose-dependent manner, and leads to the activation of apoptosis in gastric cancer cell. Interestingly, through reduction of TGF β and activation of p53 signaling pathways in HepG2 cells dihydromyricetin promotes cell apoptosis. In HepG2 cells dihydromyricetin down-regulates Bcl-2 expression and increases Bax/Bcl-2 ratio through up-regulation of p53 signaling pathway (Wu *et al*; 2013). Dihydromyricetin don't shows a selective cytotoxicity against normal cells (WI-38) but exhibit this selective cytotoxicity against non-small-cell lung cancer (NSCLC) cells (A549 and H1975). This might be related to dihydromyricetin-triggered ROS generation, which causes a mitochondria-dependent apoptosis. In addition, ROS induced ERK1/2 and JNK1/2 signaling pathways stimulated by dihydromyricetin, which can be reversed by N-acetylcysteine (Kao *et al*; 2017). Dihydromyricetin can induce apoptosis as well as autophagy in human melanoma (SK-MEL-28) cells. Dihydromyricetin potentiates ROS generation, which can be stabilized by N-acetyl-L-cysteine (NAC). Up-regulation of NF- κ B phosphorylation induced by ROS is directly related to the mechanism of dihydromyricetin-induced (Zhou *et al*; 2017). Dihydromyricetin protects against apoptosis in STZ-induced diabetic mice and induces cardiac autophagy, as indicated by up-regulation of Beclin1, Atg7, and Bcl-2 expression and LC3 II/LC3 I ratio and down-regulation of p62, caspase-3/-9 levels. Further, dihydromyricetin may improve mitochondrial functions, promote AMPK and ULK1 phosphorylation

and then inhibit diabetic cardiomyopathy (Wu *et al*; 2017).

Anti-bacterial and anti-inflammatory activity

Dihydromyricetin a flavonoid is a crude plant extract and is widely used as anti-bacterial drug for numerous uses and lessen inflammatory diseases. In addition, ampelopsin is also sensitive to inhibit other pathogenic microorganisms such as *Aspergillus flavus*, penicillium and transport streptavidin and this crude extract also shows robust inhibitory effects on *Staphylococcus aureus* and *Bacillus subtilis*. Moreover, sub-acute inflammation such as croton oil-induced auricular edema or carrageenan-induced paw edema in rats, and formaldehyde-induced paw edema in mice, as well as abdominal capillary penetrability can diminish by dihydromyricetin (Kou, Chen; 2012). Correspondingly, ampelopsin which is sequestered from *Salix sachalinensis* and it shows a tough inhibitory effect on *Cladosporium herbarum*. It is further explain by a structure–activity relationship analysis that the anti-inflammatory activity of ampelopsin is suggestively upsurge due to the hydroxyl groups at 5 different positions. Dihydromyricetin has been reported to inhibit TNF- α - induced inflammation through inactivation of NF- κ B signaling in HeLa cells. Specifically, dihydromyricetin inactivates p65 nuclear translocation and down-regulates the TNF- α - induced expression of TRAF2 and RIP1 and dephosphorylates and stops the degradation of I κ B α . In addition, the expression of NF- κ B target genes also down-regulated by dihydromyricetin, including c-IAP2, Bcl-2, TRAF1, iNOS, cyclin D1, COX-2, ICAM-1, MMP-9, and VEGF (Weili, Yousheng, 2004). IgE, and IgG1 and the infiltration of inflammatory cells into the broncho alveolar lavage. In asthmatic mouse model, ovalbumin encourages the secretion of pro-inflammatory cytokines. Dihydromyricetin has been proved to significantly decrease ovalbumin-induced inflammatory activities. Cellular damage during inflammation is mainly due to oxidative stress which is an additional contributor for this [Xu *et al*; 2017]. LPS-induced intracellular ROS levels can significantly inhibited by the administration of ampelopsin.

Phosphorylation of Akt, IKK and those of I- κ B can considerably conquer by N-acetyl-cysteine (NAC) and act as an inhibitor of ROS. The anti-inflammatory effects of dihydromyricetin are further confirmed by these pathways.

Neuroprotective activity

MicroRNAs (miRs) are proved to be the major cause for the development of Alzheimer's disease (AD). Cell tolerance to aging through induction of autophagy can be promoted by Sirt1, a direct substrate of miR-34a. In aging models, the D-gal-induced expression of miR-34a and p53/p21 pathways is down-regulated by dihydromyricetin, it up-regulates Sirt1 expression. mTOR negatively modulates autophagy activation. Activation of autophagy takes place when dihydromyricetin increase the phosphorylation of mTOR at Ser2448 and inactivate it in D-gal-induced models. In Parkinson's disease (PD), dihydromyricetin also shows neuroprotective activity in behavioral tests through diminishing of MPTP-induced cytotoxicity, GSK3 β activation dose- and time-dependently and ROS generation (Ren *et al*; 2012). Hovenia which have dihydromyricetin as its main component, and traditionally used for treatment of alcohol hangovers. Dihydromyricetin may show the shielding effects against alcohol intoxication and alcohol tolerance. The molecular mechanism is associated with competitively binding of dihydromyricetin to BZ sites on GABAARs. Long-lasting alternations in behavior and physiology is promoted due to fetal alcohol exposure (FAE), which might be related to dysfunction of GABAARs in hippocampi. In rat models, dihydromyricetin effectively stops FAE disorders through regulation of GABAARs (Liang *et al*; 2014). Dysfunction of GABAARs in neurotransmission also contributes to AD development. Dihydromyricetin decrease A β peptide production and restore gephyrin levels in transgenic (TG2576) and Swedish transgenic (TG-SwDI) mice. GABAergic transmission, and functional synapses, leading to enhancement of clinical symptoms (Liang *et al*; 2014).

Oxidative stress-mediating activity

Oxidative stress is usually a state of cellular homeostasis imbalance, in which reactive oxygen species (ROS) production overweighting the antioxidant enzyme system. Excessive ROS is responsible for mitochondria-dependent apoptosis. The mechanistic chemistry in radical searching ability of dihydromyricetin was approved in protection against mesenchymal stem cells damage. There is two model systems which confirmed the antioxidant activity of Dihydromyricetin, including cooked ground beef and soybean oil (Li *et al*; 2016). Excessive ROS mainly acts as a leading factor causative to myocardial fibrosis. Through induction of ROS production Cardiac fibroblast may be activated by angiotensin II, So promoting proliferation, and collagen synthesis. Adverse effects induced by angiotensin II were restored by dihydromyricetin, as indicating by decreased levels of MDA and ROS, increased total antioxidant capacity, and reduced expression of p22phox (a subunit of NADPH oxidase). Similar results are showed in the antioxidative effect of dihydromyricetin on attenuating angiotensin II-induced cardiomyocyte hypertrophy. On revelation to electrophiles and reactive oxygen species numerous genes coding antioxidative and detoxifying stress enzymes are drawn coordinately (Primiano *et al*; 1996) *cis*-acting element is responsible to control this coordinated response and called antioxidant-responsive element (ARE) which is present in the regulatory region of target genes. Genes that encodes a subgroup of drug-metabolizing enzymes such as glutathione-S-transferases and NADPH-quinone oxidoreductase are shown to control by ARE. Laterally with a subclass of antioxidant genes, for example glutamate cysteine ligase (GCL) and heme oxygenase (Mulcahy *et al*; 1997). The signaling system that leads to the ARE activation, and nuclear factor erythroid 2-related factor 2 (Nrf2) have recognized as a main transcriptional factor which transfers the inducer signal to ARE. Nrf2 is generally impounded in the cytoplasm by Kelch-like ECH-linked protein 1. ROS directly involved in numerous pathogenic processes comprising

inflammation and cancer is mostly. There are many antioxidants which can detoxify ROS and thus natural plant constituents, particularly antioxidants have much importance. Due to its similarity with tertiary butylhydroquinone ampelopsin retains excellent antioxidant activity (Zhang *et al*; 2003). Lipid oxidation can takes place due to free radicals in bio membranes, and the key cause for tissue damage is the destruction of the cell membrane and responsible for neurotic processes of several diseases. So exogenous impairment is directly related with free radical reactions (Zhang *et al*; 2007).

Clinical imminent

It is well demonstrated that hyperlipidemia, hepatic steatosis, and type II diabetes are mainly caused by high fat diet. In high-fat diet rats, Krebs cycles activity increases when dihydromyricetin progresses glucose uptake, promotes glucose transporter 1 (GLU1) translocation, thus leading to amelioration of insulin resistance. Dihydromyricetin reverses the decreased levels of CS, SDHA, and DLST induced by high-fat diet. Correspondingly, Dihydromyricetin also restored the increased levels of serine, leucine, asparagine, SSA, 5-L-glutamyl-alanine, and L methyl histidine. These are linked with down-regulation of phosphorylation of IRS-Ser612 and up-regulation of Akt and AMPK, resulting in reduction of G6Pase and PEPCK expression and inhibitory phosphorylation of GSK-3 β (Le *et al*; 2016). Accumulation of TG and TC in the cytoplasm of hepatocytes is most probably responsible for a nonalcoholic fatty liver disease. Dihydromyricetin showed inhibitory effects on this accumulation and ROS Lo2 and HepG2 cells. Two dihydromyricetin or two placebo capsules are applied for twice daily for three months in case of double blind trial. The serum levels of glucose, LDL-C, GGT, alanine, AST, and Apo B are significantly ameliorate by supplementation of dihydromyricetin, thus dihydromyricetin-enhanced metabolism of glucose and lipid. Moreover, the expression of CK-18 fragment, TNF- α , and FGF21 also down-regulated by dihydromyricetin (Chen *et al*; 2015). The improvement of drug sensitivity by combination chemotherapy have explained and studied

comprehensively. Though, researchers are trying to discover a distinctive compound that armors cell functions normally even when cell assembled with platinum drugs. Dihydromyricetin is mainly flavonoid extract and have many biological activities, such as rummaging free radicals, antithrombotic, anti-oxidation, anti-inflammatory, and anti-cancer effects. It is demonstrated if DHM cause the induction of apoptosis in HCC cells then it is also gives protection to liver cells to function normally. Recent researches have demonstrated that by activation of the p53/Bax pathway DHM prevents HCC cell HepG2. Furthermore, cancer cell immigration is also effected by dihydromyricetin. DHM don't show noteworthy cytotoxicity in normal cells (Zhang *et al*; 2014). Based on these discoveries, it is needed to decide whether NDP and DHM collectively cause toup-surges sensitivity of cancer cells to NDP though protecting normal cells from a noticeable injury. Now, we need to do a further study to define that DHM improve the therapeutic effects and reduces the normal cells injury and to clarify the principal molecular mechanisms.

Regulation Of Plasma lipids and blood glucose

Hyperinsulinemia can cause due to insulin resistance, The main pathogenic aspect in obesity and type 2 diabetes mellitus is the deficiency of insulin controlled glucose homeostasis₁.

The trademark of type 2 diabetes is hepatic insulin conflict. Among Western and Westernized inhabitants nutritional extremes seem to be a chiefly significant funder to the high rate of insulin conflict. Unluckily, glucose endorsement in short amount and the crucial mechanisms monitoring diet-induced insulin confrontation are only moderately understood. Lipid mixtures considered to increase plasma fatty acid quantity harm both oral glucose tolerance and insulin-stimulated glucose discarding in human being (Roden *et al*; 1996). Additionally, 3–5 h after rises in fatty acid concentrations the reduction in insulin sensitivity during such procedures only takes place and thus correlated to the degree of fatty acid rise, fatty acid

metabolite that is accumulated in skeletal muscle and liver is in charge for this phenomenon. It is further reported that dihydromyricetin also shows anti-atherosclerotic effect and it also plays an important role in order to lower the level of total cholesterol. The levels of serum totaltriglyceride and cholesterol lessens by intragastric injection of *Ampelsis grossdentata* and also cause to increase the level of serum high-density lipoprotein cholesterol in rats, so in this way ampelopsin also have hypocholesterolemic activity. 100 patients with primary hyperlipidemia were injected with a drink having dihydromyricetin 9 g/day, and quantity of triglyceride is reduced which measureable, cholesterol and plasma lipid by 72%, 42% and 28% 45 days later after injection of ampelopsin. Additionally, MDA (*i.ea* serum content) is meaningfully lessens by ampelopsin, and similarly the content of SOD is also elevated by this (Chen *et al*; 2007), therefore, ampelopsin also check the incursion of vascular smooth muscle cells and matrix deprivation, which pays to shielding measures to atherosclerosis and cancer. Moreover, intragastric dose of ampelopsin can considerably lessens the quantity of fasting blood glucose. This recommends a healing part in order to cure diabetes, which is considered as the incapability of insulin to block the making of hepatic glucose (Waltner *et al*; 2002).

Anti-hypertension effect

In recent research, norepinephrine (NE) and high K⁺ is alienate by ampelopsin so cause the induction tightening of rabbit aorta and in intestinal smooth muscle ampelopsin perform a blockage role. Recent studies demonstrated that, ampelopsin considerably inhibited the tightening related with Ca²⁺ discharge due to NE (Zhou *et al*; 1997). Though, inhibitory effects of ampelopsin on extracellular Ca²⁺ release can examine only at higher quantity. It is further explain that, voltage-dependent calcium channels (PDC) can selectively blocked by DHM dihydromyricetin play a key role as anti-high blood pressure drug. Dihydromyricetin (DHM) is a flavonoid extract which is also called Ampelopsin, it is sequestered from the

tender stem and leaves of plant species such as *Ampelopsis grossedentata*, the most common flavonoids are found in berries, grapes, vegetables, fruits herbs and in many other plants with certain anticancer activities. As the main constituent of *Ampelopsis grossedentata* DHM was labeled to have numerous pharmacological activities, such as anti-inflammatory, relieving cough, antibacterial and anti-oxidation activity, hepatoprotective as well as antihypertension hepatoprotective and anticancer effects (Zeng *et al*; 2006).

Anti-depressant effects

Major depressive disorder (MDD) extremely prevailing disease which affect shuge inhabitants around the globe. The path biological origin of MDD is not understandable, recent researches have demonstrated ranks of brain derived neurotropic factor (BDNF) in the hippocampus and neuroinflammation are thoroughly related with depression. In the progression of MDD fundamental and functional deviations in the hippocampus directly play a significant role. Reduced BDNF expression is marked in MDD patients (Nuernberg *et al*; 2016).

Those patients which are effected with MDD antidepressant drugs help to take back the countenance of BDNF. DHM a flavonoid and it's a crude plant extract which is mostly isolated from *Ampelopsis grossedentata*, and it mostly occurs in south of China that described to have many pharmacological effects, comprising anti-inflammatory, anti-tumor and anti-oxidative properties. It is previously demonstrated that DHM defends dopaminergic neurons against MPTP-induced neurodegeneration in a mouse model of Parkinson's disease by conquering the activity of glycogen synthase kinase-3 beta (GSK-3 β) (Ren *et al*; 2016) and by activating ERK1/2 and CAMP response element binding (CREB) pathway shields neurons from ischemia-reperfusion-induced apoptosis. Furthermore, a direct safety of neurons, according to recent studies it is demonstrated that DHM repressed microglia-mediated inflammation in giving safety from ischemic offence (Zhao *et al*; 2017). Previous

research also explain that inflammatory responses in RWA 264.7 is overwhelms by ampelopsin cells through preventing stimulation of NF- κ B and MAPK signaling pathways (Hou *et al*; 2015) and upgrades behavioral deficits in animal suffering from Alzheimer's disease. Moreover, activities contrary to alcohol inebriation and to recollect glucose homeostasis also described (Chen *et al*; 2015, Le *et al*; 2016, Shen *et al*; 2012).

Conclusion

Dihydromyricetin also known as ampelopsin, and isolated from *Ampelopsis grossedentata*, which grows extensively in the south of China. In this review we emphasize on biological activities of dihydromyricetin such as anticancer, apoptotic, antibacterial and anti-inflammatory, oxidative stress mediating, regulation of plasma lipids and glucose activities. Flavonoids especially ampelopsin have been used as anti-cancer drug. By hindering with numerous signaling pathways it cause the initiation of apoptosis such as ERK1/2 and p38 MAPK, Bcl2/Bax, DR4 and DR5 signaling pathways. Apoptosis can also induced by dihydromyricetin when it hinders with cyclin D and p53. Dihydromyricetin, down-regulates the expression of p53 and up-regulation Bcl-2 expression and leads to the activation of apoptosis in gastric cancer cell, furthermore, it inhibit TNF- α -induced inflammation through inactivation of NF- κ B signaling in HeLa cells. By foraging free radicals it obstructs oxidative stress and reduce lipid oxidation along with decreasing ROS levels and also regulate blood glucose and lipids.

These all exhibit that dihydromyricetin is a possible candidate for clinical promises. Though, Dihydromyricetin have limited applications due to its lower bioavailability. So, more efforts need to do for its fundamental mechanism in biology. In future experimental studies we must emphasize not only to recognize these mechanisms, but also pay attention to the progression of ampelopsin as a chemo preventive mediator for the treatment of numerous diseases.

Acknowledgments

Jilin Province Science and Technology Development Plan Project (20180201070YY).

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