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Review

Thunbergia laurifolia, a new choice of natural antioxidant to prevent oxidative stress-related pathology: A review

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Oxidative stress is an imbalance between the rate of production and clearance of oxidant, which ultimately causes the various pathologies. Antioxidants are any substances, including endogenous and exogenous antioxidant which can inhibit the oxidation reaction. Currently, antioxidant supplementation derived from natural source, especially medicinal plants is more interested. *Thunbergia laurifolia*, a Thai traditional herb, is classified as Acanthaceae family and is the most widely distributed in the northern part of Thailand. Major compounds of *T. laurifolia* are apigenin, caffeic acid, flavonoids and chlorophyll derivatives which exhibit the antioxidant properties. *T. laurifolia* extract demonstrates antioxidant properties both *in vitro* and *in vivo*. It is able to reduce Oxidative stress (OS)-induced pathology by increasing endogenous antioxidant system and reducing oxidation reaction of macromolecules. Due to high antioxidant ability and low toxicity, *T. laurifolia* is proper for application as natural antioxidant supplementation to prevent oxidative stress-related pathology.

Key words: *Thunbergia laurifolia*, acanthaceae, antioxidant, oxidative stress.

INTRODUCTION

Oxidative stress (OS) is defined as an imbalance between the rate of production and removal of oxidant. OS is the common causative factor of various diseases such as kidney diseases, cardiovascular diseases and neurodegenerative diseases by underlying mechanism of inducing oxidation reaction of lipid, protein and nucleic acid (Miranda et al., 2000; Cipollone et al., 2007; Aykanat et al., 2011). Oxidants consist of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Generally, oxygen is required in respiratory chain of mitochondria during the production of Adenosne-5-triphosphate (ATP). On the other hand, this process is produced as an unavoidable by-product called ROS and RNS. ROS/RNS are the highly reactive molecules that are able to become toxic to the cells, tissues and organs. The most important ROS are superoxide anion ($O_2^{\bullet-}$), hydroxyl radical and hydrogen peroxide. The important RNS consist of nitric oxide ($^{\bullet}NO$), peroxynitrite ($ONOO^{\bullet}$), peroxynitrous acid (ONOOH), alkyl peroxynitrites (ROONO). ROS/RNS are produced in both endogenous and exogenous sources. Endogenous sources are composed of mitochondrial leak, respiratory burst and auto-oxidation reaction. Environmental agents include radiations, xenobiotics, chlorinated compounds, cigarettes and alcohols (Young and Woodside, 2001; Bargagli et al., 2009).

ANTIOXIDANT

Antioxidants are defined as any substances which can inhibit the oxidation of a substrate, even at low concentrations (Halliwell, 1990). There are several molecules that play a role in antioxidant defense including endogenous (internally synthesized) or exogenous (consumed) antioxidants. They can be divided into 2 groups, depending on mechanism of action either as chain breaking

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antioxidants or preventive antioxidants. Preventive antioxidants reduce the rate of chain initiation and chain breaking antioxidants interfere with chain propagation. Antioxidant systems prevent uncontrolled formation of free radicals and activated oxygen species or inhibit their reactions with biological structures (Riley, 1994). *In vivo*, the principal preventive antioxidants are superoxide dismutase (SOD) which act in aqueous phase to trap $O_2^{\bullet-}$.

Hydrophilic chain breakers are found in cytosolic, mitochondrial and nuclear compartments. Hydrophobic chain breaking antioxidants are found in cell membranes where they inhibit or interrupt with chain reactions of lipid peroxidation (LPO) (Chaudiere and Ferrari-Iliou, 1999). Enzymatic antioxidants are primarily responsible for intracellular defense (Shanker et al., 2005). Non-enzymatic antioxidants are responsible for 50 to 80% of cumulative chain breaking capability possessed by blood, even though it is not their primary role. Other antioxidant compounds including ceruloplasmin, transferrin and thiols only play a limited role in antioxidant defense since their concentration in blood is low. Antioxidant resources must be constantly restored in the body. Thus, while in one particular system an antioxidant is effective against free radicals, in other systems the same antioxidant could become ineffective. For preventive way, antioxidant enzyme like SOD, catalase (CAT) and glutathione peroxidase (GPx) can prevent oxidation by reducing rate of chain initiation either by scavenging initiating free radicals or by stabilizing transition metal radicals such as copper (Cu) and iron (Fe) (Young and Woodside, 2001).

Although endogenous antioxidants play a key role to protect the cellular components against oxidative stress in human body but its capacity reduced with aging, thus dietary supplements are the vital source of exogenous antioxidants. The nutrient antioxidant deficiency causes numerous chronic and degenerative pathologies (Halliwell, 1990).

In Thailand, medicinal plants or herbs are used for the treatment of various diseases in several decades. They exhibit good effectiveness, are inexpensive, safety and availability. Current researches and financial supports have shown increased interest in their advantage. Today, extraction and development of several drugs and chemotherapeutics from these plants has been widely observed. This review focuses on the antioxidant properties of *T. laurifolia* to prevent oxidative stress-related pathology.

GENERAL CHARACTERISTICS OF *THUNBERGIA LAURIFOLIA*

T. laurifolia or Rangjued is native to Indonesia and Malaysia. It is most widely distributed in the northern part of Thailand which is classified in Acanthaceae family. It has oval-shaped leaf, narrowing to pointed tip 7 to 18 cm long and 2.5 to 6.0 cm across, that grow in opposite pairs along the stem on stalks up to approximately 6 cm long (Figure 1). The trumpet-shaped flower begins as approximately 3.5 to 4.5 cm long of broad tube, white on the outside with a yellowish throat, opens out into five rounded, pale lavender-blue petals with one larger than others. Flowers are up to 8 cm long and 6 to 8 cm across which are borne in clusters on long and drooping branches. It can be divided into 3 types depending on flower color, including white, yellow and purple. The purple type is believed to possess health benefits.

ANTIOXIDANT PROPERTIES

Oonsivilai et al. (2008) investigated the antioxidant activities and total phenolic content of *T. laurifolia* extracts by using free radical scavenging, ferric reducing antioxidant power assay (FRAP) and the Folin-Ciocalteu method. Water extraction of phenolic compounds elicits the most efficient compared to ethanol and acetone extraction. Additionally, *T. laurifolia* water extract possesses the highest antioxidant activities using free radical scavenging and FRAP assay. Moreover, *T. laurifolia* extracts show low cyto-toxicity (Oonsivilai et al., 2008). Jitbanjong and Satarug (2010) studied the alleviation of lead poisoning in the brain with aqueous leaf extract of the *T. laurifolia* in mice. Aqueous leaf extract of the *T. laurifolia* shows high levels of total phenolic content and total capacity of antioxidant which at a concentration of 100 or 200 mg/kg body weight, is able to reduce levels of malondialdehyde (MDA) in plasma and brain, and moreover, cause increases in the plasma total antioxidant capacity and GPx catalytic activity upon lead exposure. It may play an important role in reduced neuronal cell death and memory loss in lead-treated mice (Tangpong and Satarug, 2010).

Recent studies of Palipoch et al. (2011a, b) revealed protective role of *T. laurifolia* leaf extract against lead (II) nitrate-induced toxicity in fish, *Oreochromis niloticus*. Co-treatment of leaf extract of *T. laurifolia* with lead (II) nitrate reduces MDA, a lipid peroxidation biomarker and significantly increases intrinsic antioxidant including the activity of CAT in gill, level of glutathione and the activities of CAT and glutathione reductase in kidneys, and the activity of CAT in liver compared with group treated with lead only. Ultimately, it able to normalize blood chemistry, hematological and histological parameter and reduce toxicology in lead (II) nitrate-exposed *O. niloticus* (Palipoch et al., 2011a;b).

In 2012, Wonkchalee and coworkers illustrated the anti-inflammatory, antioxidant and hepatoprotective effects of *T. laurifolia* on experimental opisthorchiasis in rat. Boiled fresh and dried leaves of *T. laurifolia* possess higher total antioxidant capacity than room temperature water solution. The gross pathology of the livers indicated a reduction in thickening of the wall of the common bile duct and a reduction of inflammatory cells surrounding the intrahepatic bile ducts in *T. laurifolia*-treated group. The

Figure 1. Physical characteristics of *T. laurifolia* (purple strain).

The biochemical marker of liver [alkaline phosphatase and aspartate aminotransferase (AST)] and kidney (blood urea nitrogen and creatinine) in *T. laurifolia*-treated group remained within normal levels whereas groups administered with *N*-nitrosodimethylamine administration or infected with *Opisthorchis viverrini* exhibits high levels of serum AST about 3 to 10 folds. These results suggest that *T. laurifolia* possesses antioxidant and anti-inflammatory properties and may be applied for prevention of *O. viverrini*-associated cholangiocarcinoma (Wonkchalee et al., 2012).

The aerial part of *T. laurifolia* is isolated into 2 iridoid glucosides, including 8-*epi*-grandiforic acid and 3′-*O*-β-glucopyranosyl stibericoside, with 7 known glucosides compounds; benzyl β-glucopyranoside containing benzyl β-2′-*O*-β-glucopyranosyl, glucopyranoside, grandifloric acid, *E*-2-hexenyly-β-glucopyeanosdie, hexanol-β-glucopyranoside, 6-*C*-glucopyranosyl apigenin and 6,8-di-*C*-glucopyranosyl-apigenin. Moreover, this plant is composed of flavonoids, including casmosiin and chorogenic acids (Kanchanapoom et al., 2002). The separation profile from water extract was illustrated, with caffeic acid and apigenin as primary constituents, where as ethanol leaf extract of *T. laurifolia* was found to be good sources of chlorophyll derivatives (Oonsivilai et al., 2007).

Chlorophylls are a group of magnesium (Mg)-metallated tetrapyrroles related to porphyrins. They contain characteristic 5 isocyclic rings and long chain isoprenoid alcohol groups such as phytol and farnesol. In nature, chlorophyll *a* and *b* are predominant in higher plants, whereas chlorophyll *c, d* and *e* derivatives are found throughout various photosynthetic algae and diatomic species (Ferruzzi and Blakeslee, 2007). Endo et al. (1985) suggested that chlorophyll derivatives may be acting as electron donors as evidenced by their ability to reduce free radicals such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical (Endo et al., 1985). Chlorophyll *a* is shown to act synergistically with vitamin E by quenching tocopherol radicals, thereby enhancing the observed antioxidant effects of vitamin (Le Tutour et al., 1998). Both porphyrin structure and nature of the central metal are considered important to antioxidant activity of chlorophyll derivatives. Nickel, Cu and Mg derivatives suppressed the oxidation of linoleic acid by $O_2^{\bullet-}$, whereas Fe derivatives enhanced oxidation. Furthermore, metallochlorophyll derivatives including zinc and Cu-pheophytins exhibited significantly higher antioxidant capacity than metal-free derivatives.

The nature of chlorophyll derivatives present in fresh and processed fruits and vegetables is important when considering the antioxidant capacity of these foods (Ferruzzi et al., 2002). Caffeic acid (3,4-dihydroxycinnamic acid) is the major hydroxycinnamic acid which is present in wine. It has also been identified as one of the active antioxidants. It is an effective anti-oxidant in different *in vitro* antioxidant assays including total antioxidant activity by ferric thiocyanate method, reducing power, DPPH radical scavenging, $O_2^{\bullet-}$ radical scavenging and metal chelating activity. It is compared to

standard antioxidant compounds such as butylated hydroxyanisole, butylated hydroxytoluence, α-tocopherol, a natural antioxidant and trolox which is a water-soluble analogue of tocopherol (Gülçin, 2006). It appears to be promising as a natural antioxidant because of its ability *in vivo* of participating in the antioxidant defense system both by a direct contribution and by sparing α-tocopherol (Nardini et al., 1997). Moreover, it inhibits DNA fragmentation and caspase-3 activity during exposure to ROS and pre-incubation against sodium nitroprusside-induced toxicity in cells of fish gills. It may show beneficial antioxidant effects through other mechanisms including expression of genes for antioxidant protein (Chung et al., 2006). Apigenin, a dietary plant derived flavone subclass of flavonoid present in several fruit and vegetable is expected to play a role in cancer chemoprevention and cancer chemotherapy. It inhibits the level of LPO and significantly increases the enzymatic and non-enzymatic antioxidant defense mechanisms. From the obtained results, it is clear that apigenin is capable of inhibiting LPO and can increase the antioxidant status. Hence, they suggested that apigenin may be developed as a successful chemotherapeutic agent (Singh et al., 2004).

CONCLUSION

T. laurifolia is a medicinal plant that is most widely distributed in the northern part of Thailand. Major compounds of *T. laurifolia* are apigenin, caffeic acid, flavonoids and chlorophyll derivatives which exhibit antioxidant properties. *T. laurifolia* extract demonstrates antioxidant properties both *in vitro* and *in vivo*. It is able to reduce OS-induced pathology by increasing endogenous antioxidant system and reducing oxidation reaction of macromolecules such as lipid. Therefore, supplementation of *T. laurifolia* is one of the important approaches to prevent OS-related pathology.

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