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REVIEW: ARGINASE INHIBITORS

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ABSTRACT

The arginase enzyme catalyses the L-arginine to produce L-ornithine and urea. There are two type of arginase, Arginase1 and Arginase 2. Increasing arginase activity decrease nitric oxide by competing with NO synthases that increases concentration in L-ornithine. Current research data showed arginase inhibition helpful in cardiovascular diseases, hypertension, ischemia reperfusion injury, atherosclerosis, diabetes mellitus, asthma, cancer, immunologically-mediated diseases and leishmaniasis. Recent information on plant-derived compounds and extracts with arginase inhibitory properties. This present review new prospects in order to improve the discovery of novel arginase inhibitors from plant sources.

KEYWORDS: Arginase, L-ornithine, Catalyses, Arginase inhibitors.

Abbreviations: ARG- Arginase, NO- Nitric Oxide, NOS- nitric oxide synthase, S. *indica*- *Scutellaria indica.*

INTRODUCTION

Arginase is metalloenzyme. It was first described in 1904 by Kossel and Dakin (Kossel et al., 1904). Arginase found in bacteria, yeast, plants, invertebrates, and mammalian liver sample. (Jenkinson et al., 1996). There are two form of arginase ARG 1, ARG2. ARG1 found in liver and it is cytosolic enzyme. Arginase expressed in both endothelial and smooth muscle vascular cells (Durante, 2013). ARG 2 is found in within mitochondria and it expressed in hepatic tissue (Jenkinson et al., 1996). Some infectious pathogen express its own arginase i.e. Leishmania, Schist soma, Salmonella and Mycobacteria (Da Silva et al., 2014). ARG is urea cycle enzyme which catalyzes the final step of urea. It play important role in nitrogen

metabolism. Nitric oxide synthase hydrolyses L- Arginine into L-Citrulline and NO for vasorelaxant factor. Arginase hydrolyse L-Arginine which converted into L-ornithine and urea. It is an important for ammonia detoxification in mammals (Dimski, 1994). Arginase enzyme plays an important role in the bioavailability of L-arginine for nitric oxide synthase by substrate competition (Morris, 2002). Increasing endothelial arginase activity is decreasing nitric oxide production with competing substrate L- arginine and it regulate endothelial nitric oxide synthase activity. ARG activity is associated with impaired endothelial NO production, endothelial dysfunction, vascular stiffness. Enhancing NO production by inhibiting endothelial arginase which re-established endothelial function and aortic compliance. Consequently arginase is novel target for preventing and treating atherosclerotic vascular disease (Ryoo et al., 2008). Arginase inhibitors may use for treating vascular diseases with endothelial dysfunction (Caldwell, 2015). Arginase I in the immune response is also associated with cancer biology, it is up-regulated and promotes tumor cell growth in breast cancer (Singh et al., 2000; Chang et al., 2001). Arginase has been shown to regulate vascular cell functions primarily through impairment of NO production in cardiovascular disorder. (Vanhoutte et al., 2008).

The significance of plants is well-known to us. Plants are potential drugs and now a days there has been an increasing awareness about the importance of medicinal plants. Plants used as medicine because they are easily available, less expensive, safe, efficient and no side effects. Thousands of years plants used for medicinal purpose and therapeutically effective as new drugs for many disease such as anticancer drugs, antimicrobial drugs etc. According to World Health Organization (WHO), medicinal plants would be the best source to find variety of new drugs. Around all over the world 80% of individuals use traditional medicines. Compounds derived from medicinal plant should be investigated to better understand their properties, safety, and efficiency.

Increased activity of arginase it metabolizing the nitric oxide substrate L-arginine, it resulted reduced production of nitric oxide and endothelial dysfunction. Endothelial dysfunction play main role in the early development of atherosclerosis and vascular problems in type 2 diabetes mellitus. Improves Endothelial Function in Coronary Artery Disease and Type 2 Diabetes Mellitus by arginase inhibitor. (Shemyakin et al., 2018). Arginase is promising target for cancer prevention and treatment. NOHA inhibits arginase activity (Buga et al., 1998). Two major groups of arginase inhibitors have been distinguished the first group

includes synthetic arginase inhibitors (Ivanenkov and Chufarova, 2013). Second group includes inhibitors derived from natural products (Girard-Thernier et al., 2015). Natural products constitute a significant source of promising arginase inhibitors (Girard-Thernier et al., 2015). *Caesalpinia sappan L.*, inhibits arginases activity (Table1). (Shin et al 2011). Plant extract of *Artocarpus altilis* caused significant reduction in the activity of arginase (Akanni et al., 2014). Ethyl acetate extracts of *Byrsonima coccolobifolia* inhibit arginase (sousa et al., 2014).

Some chemical arginase inhibitors are available (Table.2) but now days so many plant based arginase inhibitors are investigated. (2S)-5, 29, 59-trihydroxy-7, 8-dimethoxy flavanone found arginase inhibitor from medicinal plant during metabolites screening (Hye Mi Hwang, 2015). *Scutellaria indica* showed significant inhibitory acivity (Sang et al., 2013). *S. indica* also used in the treatment of hemoptysis, hematemesis, anticancer, and other disease in Asia (Chiang, 1977). Caesalpinia pulcherrima bark inhibited arginase activity (Zalsabela et al., 2018). Synthetic arginase inhibitors such as nor-NOHA (Choi et al 2012), ABH (Yepuri et al., 2012), BEC (Deignan et al., 2008) were discovered. The Arginase pathway in the pathophysiology of vascular dysfunction associated with animal models of hypertension discussed in many studies (Bagnost et al., 2010; Bagnost et al., 2008), erectile dysfunction(Lorenzen et al., 2009), atherosclerosis(Ryoo et al 2006., Ming et al 2004), diabetes, (Romero et al., 2008), ageing(Santhanam et al 2008), myocardial ischemia/reperfusion(Jung et al., 2010), pulmonary artery hypertension(Chu et al 2015), cancer (Singh et al., 2000) and obesity (Chung et al., 2013). Arginase I expression was found to be up regulated with coronary heart disease (Shemyakin et al., 2012). The α-amino acid is significantly importance for inhibition (Hunter and Downs, 1945). α- amino acids a side chain residue terminated by carboxylic acid or amine confers a good level of inhibition. Arginase inhibition by L-citrulline is close to L-ornithine activity (Boucher et al., 1994). Apigenin, isovitexin, vitexin, Galangin, quercitrin, isoquercitrin, isoorientin, and orientin, fisetin, luteolin, quercetin and, 7.8-dihydroxyflavone showed inhibition of arginase in previous literature studies (Prastiwi et al., 2018). On the basis of literature studies found that flavonoid compound has an activity of arginase inhibitor (Correa et al., 2013). *Sterculia macrophylla* contain quercetin which is one of arginase inhibitor (Correa et al., 2013). 3, 4-dihydroxycinnamide useful for development of new arginase inhibitors (Thanh-Nhat Pham et al., 2016). Nω-hydroxy-nor-L-arginine (nor-NOHA) is arginase inhibitor (Custot et al., 1997). Boronic acid analogs of L-arginine formed the second generation of arginase

inhibitors (Kim et al., 2001; Baggio et al., 1999). Arginase 1 plays a significant role in immune response, and previous work shows that arginase inhibition blocks the growth of lung carcinoma in a murine model (Rodriguez et al., 2004; Rodriguez et al., 2002; Rodriguez et al., 2003). Inhibition of arginase is important for the treatment of various disease including cardiovascular diseases (Arraki et al., 2017). Arginase plays important role in hypertension. The possible cardiovascular therapeutic effects of a long-term treatment with an arginase inhibitor in hypertensive rats with fully developed hypertension (Bagnost et al., 2010). Recently the drug discovery programs identified α–α-disubstituted amino acid based arginase inhibitors [such as (R)-2-amino-6-borono-2-(2-(piperidin-1-yl) ethyl) hexanoic acid]. Arginase inhibition activity restores endothelial function in atherosclerosis, myocardial ischemia, hypertension, and aging (Ryoo et al., 2008). Arginase inhibition plays a role in vascular dysfunction by restoring endothelial vasorelaxant function, reducing vascular stiffness, and markedly reducing atherosclerotic plaque burden as previously reported by (Ryoo et al., 2011).

Now a days Investigators are focusing on identification of plant derived compounds with arginase inhibitory such as piceatannol-30-O-β-Dglucopyranoside (PG) (Steppan et al., 2013). Arginase inhibition enhances obesity-induced abnormalities in hepatic lipids (Devrim et al., 2008). Phenolic compounds are present in rhizomes which are responsible for potent arginase inhibition (Akinyemi et al., 2016). The role of arginase in hypertension was described by various authours (Rodriguez et al., 2000). Oral treatment of arginase inhibitors prevents the development of hypertension and lowers the blood pressure (Bagnost et al., 2008). Arg1 is a key mediator of immune suppression and it inhibited Arg1 with CB-1158 shifts and reducing tumor growth. CB-1158 blocked arginase it will be effective therapy in multiple types of cancer (Steggerda et al., 2017).

Table 1: Inhibition of arginase by plants.

No.	Plant name	Extract	Plant part
1.	*Scutellaria indica*	Methanol extract	Whole plant
2.	*Caesalpinia pulcherrima*	Methanol extract	Stem and Bark
3.	*Sterculia macrophylla*	Methanol extract	Leaves
4.	*Agaricus bisporus*	Aqueous extracts	Fruit
5.	*Byrsonima coccolobifolia*	Ethyl acetate extracts	Leaves and Stems
6.	*Caesalpinia sappan*	Ethylacetate Extract	lignum
7.	*Pitanga*	Supercritical extract with ethanol as co-solvent	Seed
8.	*Cesalpinia sappan*	Ethyl acetate extract	Heartwood

9.	*Zingiber officinale*	Aqueous extracts	Rhizom
10.	*Cyperus eragrostis*	Methanol extract	Seeds
11.	*Carex appressa var. virgata*	Methanol extract	Seeds
12.	*Carex cuprina*	Methanol extract	Roots
13.	*Curcuma longa*	aqueous extracts	
14.	*Artocarpus altilis*	Methanol extract	Stem bark
15.	*Ficus glomerata*	Petroleum ether extract	Stem bark
16.	*Korean red ginseng*	Water extract	Root
17.	*Yucca schidigera*	Water extract	Whole plant
18.	*Cecropia pachystachya*	Ethanolic extract	Leaves
19.	*Byrsonima coccolobifolia*	Ethanolic extract	Leaves and Stems
20.	*Rheum undulatum*	Ethanolic extract	Rhizom

Table 2: Arginase inhibitors.

Plant derived Arginase inhibitors	**Ref**	**Synthetic arginase inhibitors**	**Ref**
Chlorogenic acid	Jiang et al., 2000	NOHA	Singh et al., 2001
Piceatannol	Wolter et al., 2002	nor-NOHA	Bak et al., 2008
Wogonin	Li et al., 2009	L-norvaline	Chang et al., 2001
(2S)-5,7-dihydroxy-8,20-dimethoxyflavanone	Tomimori et al., 1985	CB-1158	Works et al., 2016
Apigenin	Loo et al., 1986	S-(2-boronoethyl)-l-cysteine	The Penn State Research Foundation, 2011
(2S)-5,20,50-trihydroxy-7,8-dimethoxyflavanone	Miyaichi et al., 1987	2(S)-amino-6-(borono) hexanoic acid)	Rijksunversiteit Groningen, 2006
naringenin-5-O-b-D-glucopyranoside	Ibrahim et al., 2003	(2S,3S)-3-amino-2[3-(dihydroxyboranyl)propyl] tetrahydrofuran-3-carboxylic acid)	Mars, Inc, 2010
(2S)-5,50-dihydroxy-7,8-dimethoxyflavanone-20-O-bD-glucopyranoside	Botha et al., 1981	(2S)-2-amino-6(dihydroxyboryl)-2-[cis-3-(4fluoro-1-naphthyl)methyl]amino] cyclobutyl]hexanoic acid)	Mars, Inc, 2011
piceatannol-3′-O-β-D-glucopyranoside	Woo et al., 2010	(N5(benzyloxycarbonyl)-N2-(tertbutoxycarbonyl)-l-thiocitrulline tert-butyl ester)	Christian-Albrechts-Universitat zu Kiel, 2009
Virgatanol	Arraki et al., 2017	(2-[4-(dihydroxyboranyl)butyl] lysine)	The Trastees of University of Pennsylvania, Arginetix, inc, 2009
Isoquercitrin	Sousa et al., 2014	(6-(dihydroxyboranyl)2-[2-(piperidin-1-yl)ethyl]-lnorleucine dihydrochloride)	Mars, Inc, 2010
Catechin	Sousa et al., 2014		
Epicatechin	Sousa et al., 2014		

Plant-derived constituents, mainly polyphenols have the potential to inhibit arginase activity. Pharmacological arginase inhibitors has promising potential for new drugs for the treatment of cardiovascular diseases, asthma or infectious diseases. Arginase inhibition in the treatment of several human diseases. Plants compounds are rich source active agent (Newman et al., 2012), and it has chemical and biological diversity because of that, discovery of new compounds of arginase inhibitors is needed. In the end of this review with the suggestions improve the discovery of novel arginase inhibitors.

CONCLUSION

Discovery of arginase was one century ago. This enzyme hydrolyses L-arginine into urea and L- ornithine. Arginase inhibitory effect of α-amino acids was studied. Arginase involvement is linked to low NO level because NOS and arginase both are share the same substrate. All collected data suggest that the development of arginase inhibitors is of good therapeutic in various human diseases. Few active chemical arginase inhibitors are available. In this review provide the important information that plants contain natural arginase inhibitors. Plant-derived compounds polyphenols and some other metabolites such as steroids, tannins, alkaloids and terpenoids are important sources of arginase inhibitors. The present review aims at summarizing the available data about arginase inhibitors.

CONFLICT OF INTEREST

The authors do not have any kind of conflict of interest affecting the compilation of the current knowledge in this area for writing this review.

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