Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[2] January 2020 : 160-163

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

Pharmacological effects of Polyphenols in Renin Angiotensin System: A Review

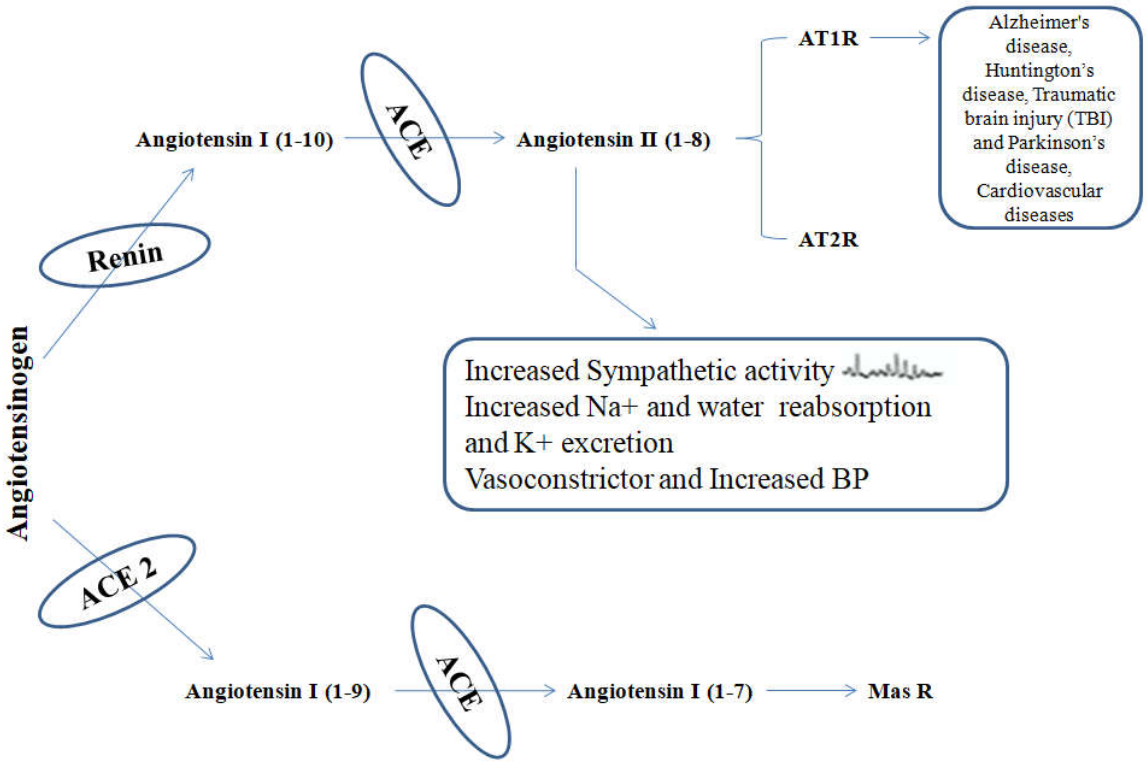
Vibhav Varshney*
Division of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura-281 406
*Email: Vibhav.math@gmail.com

ABSTRACT
The renin-angiotensin-aldosterone system (RAAS), is a hormone system, plays a critical role in regulating blood volume and systemic vascular resistance, which collectively influence cardiac output and arterial pressure. Several drugs have been developed to target RAAS to alleviate cardiovascular diseases. Additionally, it has been suggested that renin-angiotensin systems (RAS) exhibits number of physiological functions other than cardiovascular activities in different tissues such as kidney and nervous systems. Therefore, RAS exhibits pleiotropic action in mammalian physiology. Further in this context, it has been documented that RAS targeted drugs, when is intended to use for neurological disorders, exerts several unwanted serious side effects. Thus, there is a need to develop an alternate and complementary therapeutic strategy to target RAS to manage such disorders. It has been well documented that most of the natural foods and their supplements possess polyphenolic compounds that are reported to have RAS-targeted activity to exert respective therapeutic activities against diseases. It has been reported that polyphenoles such as quercetin, catechin related compound, delphinidin and cyanin act through modulating classical RAS by inhibiting ACE activity. Moreover, naringin, hesperidin and taxifolin also reported to have therapeutic activity against cognitive dysfunction. Hence, the present review provides better insight in the pharmacological use of polyphenols in the management of several peripheral and central disorders.
Keywords: Flavonoids, Angiotensin converting enzyme (ACE), RAS.

Received 23.07.2019 Revised 15.11.2019 Accepted 01.12.2019

INTRODUCTION

Rennin angiotensin aldosterone system (RAAS) is one of the classical endocrine systems that maintain several physiological functions including cardiovascular, fluid homeostasis and kidney[1].The classical axis of RAAS constitutes ACE/Ang II/AT1R that plays an important role in maintaining the physiological functions. In this system, rennin cleaves angiotensinogen to Angiotensin-I, which is further processed by ACE to Angiotensin-II, a potent vasoconstrictor, which mediate its action via AT1R [2][fig. 1]. It has been well validated that RAAS is considered as one of the major target in the treatment of several metabolic disorders however drugs targeting this system possess serious side effects. It is well documented that RAS is not limited to periphery as it exists in other tissues such as brain[1].In support to the above fact, it has been illustrated that by chronic activation of RAS can alter other physiological functions[1].It has been well hypothesized that drugs targeting RAS in other tissues including brain could alleviate their respective abnormalities. However, experimental studies also report that these drugs can exhibit serious adverse effects in mammalian physiology. Moreover, there are several herbal polyphenols has been reported as therapeutic agents through exhibiting their pharmacological activities perhaps through RAS with limited or no adverse effects. Hence, a comprehensive review is attempted for polyphenols on several RAS.



[Fig.1] Classical and alternative pathways of RAS. ACE and ACE-2 are involved in maintain various functions through production of Ang II and Ang (1-7) by acting on their receptors.

RELATIONSHIP BETWEEN RAS AND NEUROLOGICAL FUNCTION

RAS plays a significant role in the pathogenesis of several neurodegenerative disorders such as Alzheimer's disease [AD], Huntington's disease, traumatic brain injury [TBI] and Parkinson's disease. It is evidenced that RAS play a major role in pathophysiology of ADthrough increased level of ACE in certain brain regions such as hippocampus, frontal cortex and caudate nucleus[3]. In experimental studies, it has been reported that Ang-II injection facilitates the amyoid beta aggregation in rats and thus cause dementia[4].Biologically active peptide Ang-II is pleotropic neuroregulator that perform several physiological functions through the stimulation of brain AT1R and AT2R [5]. It is also established that AT1R has participated in the amyloid beta production through non amyloidgenic pathway [6]. Stimulation of classical RAS axis induces the several neurodegenerative pathways such as reactive oxygen species [ROS] production, inflammatory response and apoptosis [7].Although Ang [1-7] is part of RAS counteracting the Ang II actions via its MAS receptor, which is abundantly, located in different brain regions including hippocampus, olfactory bulb, amygdala, nucleus of the solitary tract[8].These observations emphasize the fact that there is a strong relationship between RAS and neurological activities.

THERAPEUTIC POTENTIAL OF POLYPHENOLS IN RAS

As the RAS associated with peripheral and brain disorders so that RAS is major pathway to treat such type of disorders.ACE is limiting factorfor theRAS induces vasoconstriction and high blood pressure. Several RAS targeted drugs such as ACEIs and ARBs have serious side effects. Enzyme and peptide synthesis in different steps in RAS system targeted drugs such as Captopril, Enalpril and Lisinopril are the ACEIs induce adverse effect such as dizziness coughing and angioneuretic edema when intended to use [9]. However, Talmisartan and Olmisartan are reported to have frequently dizziness,upper respiratory infections, back pain, sinusitis and diarrhea[10]. Polyphenols are phytochemical compounds present in plants perform different biological activities. These polyphenolic compounds are flavonoids responsible for antioxidants and anti-inflammatory effect in cell before their vulnerability [11]. The by-products of the oxidative stress [ROS/RNS]can initiate the inflammatory process resulting in synthesis and secretion of proinflammatory cytokines. Oxidative stress and inflammation are considered major alternative pathways contributing to the pathogenesis of several diseases induced by the RAS in peripheral and brain diseases such as hypertension, cardiac arrhythmia, diabetes nephropathy stroke, metabolic disorders,

Alzheimer's [12]. It has been documented that polyphenols are anti-inflammatory and antioxidants [13]. However, polyphenols are potential strategy for treatment for such disease without any adverse effect. Many polyphenols are reported [Table no.1] their activity for the treatment of several disorders.

Table No. 1:Potential Polyphenols in the management of various disease

S.No.	Polyphenols	Mechanism	Reference
1.	Catechin	Inhibition of Renin a crucial enzyme of RAS in treatment of hypertension.	Li., *et al.*[2013]
2.	Anthocyanins	Inhibition of ACE against Hypertension	Kwon *et al.*[2010]
3.	Silymarin	Exhibit Antioxidant and anti-inflammatory activity through the modulation of TNF-α and MDA and also target RAS in effective for the treatment of Diabetic nephropathy	Fallahzadeh *et al.*[2012]
4.	Quercetin	It reduce oxidative stress, interfere with the RAS (ACEIs), and /or improve endothelial through balance between ET-1and NO	Loke., *et al.*[2008]
5.	Rutin	Exhibit neuroprotection and helpful in management of Alzheimer disease through antioxidant and anti-inflammatory activities	Budzynska *et al.* [2019]
6.	Total flavonoid extract from Dracoephalum moldavica L. (TFDM)	Ameliorate cognitive impairment through reduced Aβ deposition and redox balance	Liu *et al.*[2018]
7.	Myricetin	It improves cognitive dysfunction by inhibition of AchE and inhibiting the transferrin receptor1 (Trf1)	Wang *et al.*[2017]
8.	Breviscapine	Effective against Aβ formation, as an antioxidant	Xia *et al.*[2017]

CONCLUSION

In conclusion, it can be presumed that polyphenols could be a potential therapeutic option in the management of several pathophysiological conditions. Further, the derivatives of these polyphenols can be studies for the better therapeutic option in the management of several disorders.

REFERENCES

1. Lazaroni TL, Raslan AC, Fontes WR, de Oliveira ML, Bader M, Alenina N, *et al.* Angiotensin-(1-7). (2012. Mas axis integrity is required for the expression of object recognition memory. Neurobiology of Learning and Memory.97(1):113-123.
2. Li F, Takahashi Y, Yamaki K. (2013). Inhibitory effect of catechin- related compounds on rennin activity.Biomedical Research.34(3):167-171.
3. Savaskan E, Hock C, Olivieri G, Bruttel S, Rosenberg C, Hulette C, *et al.* (2001). Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. Neurobiology of Aging. 22(4):541–546.
4. Zhu D, Shi J, Zhang Y, Wang B, Liu W, Chen Z, *et al.*(2011). Central angiotensin II stimulation promotes beta amyloid production in Sprague Dawley rats.PLoS One.6(1):1-9.
5. Saavedra JM. (2016). Evidence to consider angiotensin II receptor blockers for the treatment of early Alzheimer's disease. Cellular and Molecular Neurobiology.36(2):259-279.
6. Kanare AM, Wagner A, Küppers J, Gütschow M, Postina R, Kojro E. (2017). Crosstalk between angiotensin and the non-Amyloidgenic pathway of Alzheimer's amyloid precursor protein. FEBS Journal.284(5):742-753.
7. Cetin F, Yazihan N, Dincer S, Akbulut G. (2013). The effect of intracerebroventricular injection of beta amyloid peptide (1-42) on caspase-3 activity, lipid peroxidation, nitric oxide and NOS expression in young adult and aged rat brain. Turkish Neurosurgery.23(2):144-150.
8. Tallant EA, Ferrario CM, Gallagher PE.(2005). Angiotensin-(1–7) inhibits growth of cardiac myocytes through activation of the mas receptor. American Journal of Physiology Heart and Circulatory Physiology.289(4):H1560–H1566
9. Israili ZH, Hall WD. (1992). Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Annals of Internal Medicine.117(3):234-42.
10. Sabbah ZA, Mansoor A, Kaul U. (2013). Angiotensin Receptor Blockers - Advantages of the New Sartans. Journal of Association of Physicians of India.61(7):464-70.

11. Kumar S, Pandey AK. (2013). Chemistry and biological activities of flavonoids: an overview.The Scientific World Journal. doi: 10.1155/2013/162750 2013.16.
12. Sant'Anna LS, Merlugo L, Ehle CS, Limberger J, Fernandes MB, Santos MC, *et al.*(2017). Chemical Composition and Hypotensive Effect of Campomanesia xanthocarpa. Evidence-Based Complementary and Alternative Medicine. doi.org/10.1155/2017/1591762.11
13. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. (2016). Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? Oxidative Medicine and Cellular Longevity. http://dx.doi.org/10.1155 /2016/7432797.
14. Kwon EK, Lee DY, Lee H, Kim DO, Baek NI, Kim YE, *et al.*(2010). Flavonoids from the buds of Rosa damascena inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme a reductase and angiotensin I-converting enzyme. Journal of Agriculture and Food Chemistry. 58(2):882-886.
15. Fallahzadeh MK, Dormanesh B, Sagheb MM, Roozbeh J, Vessal G, Pakfetrat M, *et al.*(2012). Effect of addition of silymarin to reninangiotensin system inhibitors on proteinuria in type 2 diabetic patients wi th overt nephropathy:a randomized, double-blind, placebo-controlled trial. American Journal of Kidney Disease. 60(6):896-903.
16. Loke WM, Hodgson JM, Proudfoot JM, McKinley AJ, Puddey IB, Croft KD. (2008). Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduceendothelin-1 acutely in healthy men.The American Journalof Clinical Nutrition.88 (4):1018–1025.
17. Budzynska B, Faggio C, Kruk-Slomka M, Samec D, Nabavi SF, Sureda A, *et al.*(2019).Rutin as neuroprotective agent: from bench to bedside.Current Medicinal Chemistry. 26(27)5152-5164.
18. Liu QS, Jiang HL, Wang Y, Wang LL, Zhang JX, He CH, *et al.* (2018). Total flavonoid extract from *Dracoephalum moldavica* L. attenuates β-amyloid-induced toxicity through anti-amyloidogenesic and neurotrophic pathways. Life Sciences. ;193:214-225.
19. Wang B, Zhong Y, Gao C, Li J. (2017). Myricetin ameliorates scopolamine-induced memory impairment in mice via inhibiting acetylcholinesterase and down-regulating brain iron.Biochemical Biophysical Research Communications.;490(2):336-342.
20. Xia H, Wu L, Chu M, Feng H, Lu C, Wang Q, *et al*. (2017).Effects of breviscapine on amyloid beta 1-42 induced Alzheimer's disease mice: A HPLC-QTOF-MS based plasma metabonomics study. J Chromatography B.1057:92-100.

CITATION OF THIS ARTICLE

V Varshney. Pharmacological effects of Polyphenols in Renin Angiotensin System: A Review. Bull. Env. Pharmacol. Life Sci., Vol 9[2] January 2020 : 160-163