International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395 -0056
Volume: 03 Issue: 10 | Oct -2016 www.irjet.net p-ISSN: 2395-0072

# Impact Of Polyphenols On Cholesterol Esterase Inhibition – A Mini Review

**T.Sathish Kumar[1], M.Aishwarya[1], K.Archana[1], S.Divya[1], S.Seetha Lakshmi[1]**

[1]*Department of Biotechnology, Kumaraguru College of Technology, Coimbatore – 641 049, Tamil Nadu, India*

---

**Abstract -** *Cholesterol, one of the most essential components of cell adopted for executing various physiological functions such as maintenance of cell membrane fluidity, synthesis of sex hormones, and bile acid and salt, is synthesized in adequate amount by liver. But, increased level of dietary cholesterol may increase the blood cholesterol level; a precursor for the cause of hypercholesterolemia that leads to various cardiovascular diseases. Pancreatic cholesterol esterase is the major enzyme responsible for the hydrolysis of dietary cholesteryl esters to free cholesterol that are absorbed by the body. Hence, various mechanisms have been explored to inhibit the cholesterol esterase in order to prevent the entry of dietary cholesterol into the blood and thereby, maintenance of normal homeostasis. One such novel approach is the utilization of plant based polyphenols for the inhibition of the above said enzyme.*

***Key Words***: **Cholesterol esterase, Polyphenols, Hypercholesterolemia, Cardiovascular disease.**

## 1.INTRODUCTION

Cholesterol is one of the vital component of cell membrane is essential for the execution of various functions of a cell. Cholesterol is important for the production of steroid hormones, bile salts, vitamin D, etc., and is derived from the dietary sources and also synthesized endogenously in liver. Hence, uptake, endogenous synthesis and catabolism of cholesterol should be balanced for an effective maintenance of its level in the serum. Therefore, an increase in the serum cholesterol level can cause hypercholesterolemia and prolonged condition leads to the occurrence of various types of cardiovascular diseases. There are various mechanisms to prevent hypercholesterolemia and one such strategy is the inhibition of cholesterol esterase (CEase), an enzyme that hydrolyzes the cholesterol ester to free fatty acid and cholesterol. The inhibition of cholesterol esterase prevents diseases such as hypercholesterolemia, dyslipidemia and related diseases such as atherosclerosis, cardiac arrest, stroke and heart attack. Recent approach is the recruitment of plant based polyphenolics for the inhibition of cholesterol esterase and thereby, the prevention of the above cited diseases can be inhibited by polyphenols from plant sources.

### 1.1 Cholesterol esterase

Cholesterol esterase is a polymeric enzyme that is produced as a component of the pancreatic juice by acinar cells of pancreas [1]. The human body cannot absorb the cholesterol esters in the diet and thus, cholesterol esterase in pancreatic juice play a vital role in the hydrolysis of cholesterol ester to cholesterol and free fatty acids. The formed unesterified cholesterol can then be easily absorbed by the intestine into the blood stream. The gene that encodes for cholesterol esterase consists of 11 exons and 10 introns with a length of 9.2 Kb [2]. The cholesterol esterase is a glycoprotein with a molecular weight of 65-69 kDa [3] with 747 amino acids. The active sites are S194, H435, and D320. Thus, the function of cholesterol esterase is to control the bioavailability of cholesterol from dietary cholesterol esters and to aid in transport of free cholesterol to the enterocyte.

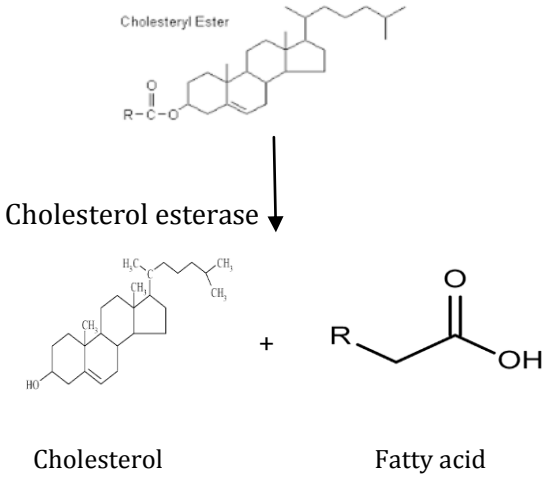



**Fig -1: Action of cholesterol esterase on cholesteryl ester**

## 2. MEDICINAL PLANTS AND ITS IMPACT

Medicinal plants normally produce different types of secondary metabolites/ phytochemicals that are important to cure or prevent a disease and also to defend the attack by various types of microorganisms and insects. Out of 350 000 plant species identified so far, about 35,000 are used worldwide for medicinal purposes and less than about 0.5% of these have been chemically investigated [7]. In the year 2001, about 122 different compounds identified for the treatment of various ailments are derived from the traditional medicinal plants [12]. According to WHO, 80% of the modern drugs are derived from the herbs and plants.

Any part of the plant can possess the medicinal value; this includes the stem, leaves, bark, flower, peel, flesh of the fruit and root. The medicinal uses of some Indian plants have been tabulated below:

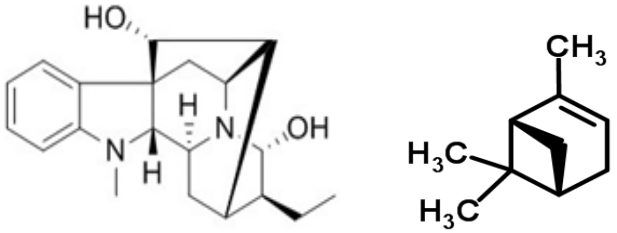
**Table 2.1: Medicinal plants and its uses**

| S.No | Common name | Botanical name | Part of the plant | Uses |
|---|---|---|---|---|
| 1. | Chameleon Plant | *Houttuynia cordata* | Leaf extract | Dysentery |
| | | | Rhizome | Stomach ulcer |
| 2. | Java pepper | *Piper cubeba* | Dried cubebs | Oral and dental diseases, fever and cough. |
| 3. | Elephant foot yam | *Amorphophallus paeoniifolius* | Corm | Treatment of Bronchitis, asthma, abdominal pain, emesis, dysentery, enlargement of spleen, piles |
| 4. | South-Indian Uvaria | *Uvaria narum* | Root and leaves | To treat intermittent fever, biliousness, jaundice, rheumatic fever |
| | | | Root bark | To control fits during the time of pregnancy |
| 5. | Kumarika | *Smilax ovalifolia* | Root | Venereal disease, urinary complaints and dysentery |
| 6. | Malabar chlorophtum | *Chlorophytum malabaricum* | Root | Diuretic |
| 7. | Jambu | *Allium stracheyi* | Whole plant | Wound healing, jaundice. |
| 8. | East Indian arrow root | *Curcuma anhustifolia* | Whole plant | Used as non-irritating diet in certain chronic diseases. |
| 9. | Turmeric | *Curcuma longa* | Rhizome | Anti-inflammatory, antioxidant |
| 10. | Opium poppy | *Papaver somniferum* | Dry opium | Analgesic, astringent, antispasmodic. |

## 3. SECONDARY METABOLITES

Plants produce large number of compounds that are required for their survival. These compounds are classified as primary and secondary metabolites. Generally, the secondary metabolites defend the plants against predators and help the plant to withstand the abiotic stress and some are pheromones that attracts insect for pollination. These secondary metabolites have medicinal value and include alkaloids, terpenoids, glycosides, polyphenols, phenolic acid, phenazines, polyketides, saponin, etc.

Alkaloids are nitrogen containing chemical compounds that are produced by the medicinal plants. The alkaloids may be colored or colorless and some are volatile. The alkaloids are produced by 10 – 25% of the higher plants. Nicotine, berberine, cyclopamine, Lupinine are some of the examples of plant alkaloids. Many drugs are produced by the structural modifications of alkaloids. Applications of certain alkaloids are: Ajmaline and quinidine have antiarrhythmic property, vinblastine and vincristine have the antitumor property, morphine has analgesic property, emetine is used as antiprotozoal agent, and anabasine is used as insecticide [19].

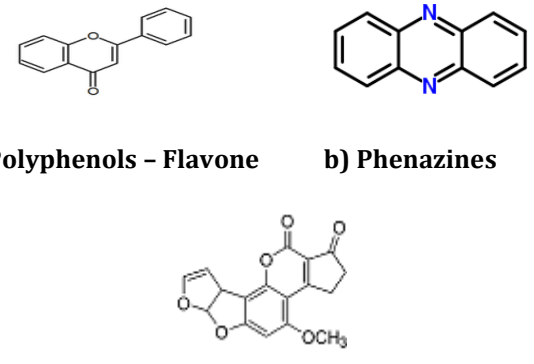



**a) Alkaloid – Ajmaline** **b) Terpenoids - Pinene**

**Fig -2: Secondary metabolite (i)**

Terpenoids or terpenes are found mostly in the essential oil of the plants, with strong odour. They protect the plants from the attack of herbivores and are also used in aromatherapy. Terpenes are derived from the isoprenoid units. Pinene, linalool, myrcene, farnesol, cembrene, squalene and lycopene are some of the terpens found in the plants.

Polyphenols are phytochemicals with antioxidant property that defend the plants from ultraviolet radiations. Based on the number of phenol rings they are classified as flavonoids, phenolic acids, lignans, and stilbenes. They have many potent applications like prevention of cancer and angiogenesis [22], protection of cardiovascular system, support the normal blood pressure and sugar levels, and reduction of inflammation. The polyphenols are rich in tea and they contribute to the astringency. Green tea, black tea, red wine, olive oil and chocolates are some of the sources of polyphenols [23].




**a) Polyphenols – Flavone** **b) Phenazines**

**c) Polyketide - aflatoxin**

**Fig- 3: Secondary metabolite (ii)**

Polyketides are the biologically active complex compounds that are important for the survival of the producing organisms. Many pharmaceuticals are derived from polyketides. They are antifungal, antibiotic and antitumor agents. Doxycycline, erythromycin and aflatoxin are some examples of polyketides.

### 3.1. POLYPHENOLS

Polyphenols present in fruits and vegetables are the one that contribute the taste, color, odor and astringency. Thus fruits like pears and berries have 200-300 mg polyphenols/100 g fresh [26]. They have beneficial effects on human health such as protection against cancer, osteoporosis and cardiovascular diseases. On the basis of number of phenol rings they are classified as flavonoids, phenolic acids, lignanas, stilbenes.

**i) Phenolic acid:**

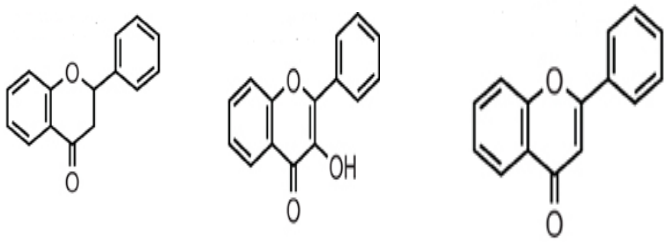
The phenolic acids are aromatic compounds that maybe benzoic acid derivative or cinnamic acid derivative. Phenolic acid are found in coffee, dry fruits and berries [27]. In plants they stimulate the production of IAA and act as signalling molecules [28]. Caffeic acid, ferulic acid, sinapic acid, benzoic acid and gallic acid are the kind of phenolic acids that are found in plants. They protect the plants from the predator microorganisms that contribute to their antimicrobial and antioxidant property. They induce apoptosis, regulates carcinogen metabolism and inhibits DNA binding and cell adhesion [29].


**a) Cinnamic acid derivative** **b)benzoic acid derivative**

**Fig -4: Phenolic acids**

**ii) Flavonoids:**

Flavonoids are non-nitrogenous polyphenols with the basic structure of two aromatic rings (C6) and one heterocyclic ring which contain an oxygen atom. They play a vital role in floral pigmentation which is crucial to attract pollinators and some inhibit the growth of microorganism. They are classified as flavonols, flavanones, flavones, anthocyanins and isoflavones. They have various properties such as antimicrobial, anti-inflammatory, anti-ulcer, anti-thrombotic, antioxidant, anticancerous and cardiotonic property. In addition they can lower the cholesterol level and can protect liver from hepatitis.



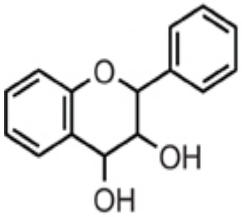
a)Flavanone



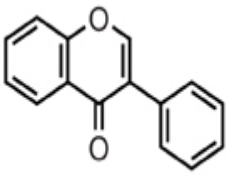
b) Flavone



c)Flavanol



d) Flavondiol



e) Isoflavone

**Fig- 5: Flavonoids**

## 4. CHOLESTEROL ESTERASE INHIBITION

Pancreatic cholesterol esterase is also known as bile salt-activated lipase. It plays a vital role in hydrolysis of dietary cholesterol esters to fatty acids and free cholesterol. The enzyme is a catalytic triad (Ser194-His435-Asp320). Moreover, they have the ability to convert LDL into smaller subspecies i.e., denser and cholesterol rich compounds [32]. This may cause an increase in the level of plasma cholesterol which eventually leads to cardiovascular disease and atherosclerosis.

Drugs such as lovastatin, amlodipine, nifedipine and simvastatin are effective in inhibiting the CEase. It has been reported that the cardiovascular drugs along with benzodiazepines binds to the active site of the catalytic triad, thereby inhibiting the enzyme activity.

The extracts of some plants and fruits have shown potent inhibition of cholesterol esterase. For example, it has been reported that, the leaf extract of senna and the flower extract of safflower have inhibited the cholesterol esterase with $IC_{50}$ value of 2.54 and 1.70 mg/ml, respectively [34]. Camellia sinensis have also been reported to inhibit the CEase. This is due to the presence of polyphenols i.e, flavonoids. The flavanoids irreversibly bind with the enzyme in its active pocket at serine 194. The effective inhibition is due to the ability of flavanoids to act as substrate ahead of cholesterol esters [35]. Thus, polyphenols from various fruits such as grapes, Hibiscus sabdariffa, Moringa oleifera, etc have the ability to inhibit CEase.

## 5. CONCLUSION

There are various methods or treatment to prevent hypercholesterolemia and related cardiovascular diseases. The use of chemical drug is effective but may equally have a side effect. Hence, the natural means of inhibition is preferable. One such natural method is the use of polyphenols from various plant sources to inhibit the pancreatic cholesterol esterase. The secondary metabolites i.e. polyphenols prevents the hydrolysis of dietary cholesteryl esters by binding to the active sites of CEase and leads to the prevention of various cardiovascular diseses.

## REFERENCES

[1] Labow, R. S., Adams, K. A., & Lynn, K. R. (1983). Porcine cholesterol esterase, a multiform enzyme. *Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology*, *749*(1), 32-41.

[2] Kumar, B. V., Aleman-Gomez, J. A., Colwell, N., Lopez-Candales, A., Bosner, M. S., Spilburg, C. A., ... & Lange, L. G. (1992). Structure of the human pancreatic cholesterol esterase gene. *Biochemistry*, *31*(26), 6077-6081.

[3] Hyun, J., Treadwell, C. R., & Vahouny, G. V. (1972). Pancreatic juice cholesterol esterase: Studies on molecular weight and bile salt-induced polymerization. *Archives of biochemistry and biophysics*, *152*(1), 233-242.

[4] Heidrich, J. E., Contos, L. M., Hunsaker, L. A., Deck, L. M., & Vander Jagt, D. L. (2004). Inhibition of pancreatic cholesterol esterase reduces cholesterol absorption in the hamster. *BMC pharmacology*, *4*(1), 5.

[5] Sawant, A. M., Shetty, D., Mankeshwar, R., & Ashavaid, T. F. (2008). Prevalence of dyslipidemia in young adult Indian population. *JAPI*, *56*(2), 99-102

[6] LM McCune, T Johns - Journal of Ethnopharmacology, 2002 – Elsevier. Antioxidant activity in medicinal plants associated with the symptoms of diabetes mellitus used by the Indigenous Peoples of the North American boreal forest

[7] Rao, V. R., & Arora, R. K. (2004). Rationale for conservation of medicinal plants. *Medicinal plants research in Asia*, *1*, 7-22.

[8] Houghton, P. J. (1995). The role of plants in traditional medicine and current therapy. *The Journal of Alternative and Complementary Medicine*, *1*(2), 131-143.

[9] Stepp, J. R. (2004). The role of weeds as sources of pharmaceuticals.*Journal of ethnopharmacology*, *92*(2), 163-166.

[10] Solecki, Ralph S. (November 1975). "Shanidar IV, a Neanderthal Flower Burial in Northern Iraq". *Science*. **190** (4217): 880–881.

[11] Pittler, M.; Abbot, NC; Harkness, E.F.; Ernst, E. (2000). "Location bias in controlled clinical trials of complementary/alternative therapies". *International Journal of Epidemiology*. **53** (5): 485–489.

[12] Pan, S. Y., Litscher, G., Gao, S. H., Zhou, S. F., Yu, Z. L., Chen, H. Q., ... & Ko, K. M. (2014). Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources.*Evidence-Based Complementary and Alternative Medicine*, *2014*.

[13] Biswas, R. N., & Temburnikar, S. O. (2003). Safed Musali (Chlorophytum Species)—A Wonder Drug in the Tropical Zone. In *XIth World Foresty Conference*.

[14] Bisht, B. S., & Nayar, S. L. (1960). Pharmacognostic study of the rhizome of Curculigo orchioides Gaertn. *J. Sci. Ind. Res. C*, *19*, 252-4.

[15] Ammon, H. P., & Wahl, M. A. (1991). Pharmacology of Curcuma longa. *Planta medica*, *57*(01), 1-7.

[16] Samal, P. K., Shah, A., Tiwari, S. C., & Agrawal, D. K. (2004). Indigenous health care practices and their linkages with bio-resource conservation and socio-economic development in central Himalayan region of India. *Indian Journal of Traditional Knowledge*, *3*(1), 12-26.

[17] Chhetri, D. R., Basnet, D., Chiu, P. F., Kalikotay, S., Chhetri, G., & Parajuli, S. (2005). Current status of ethnomedicinal plants in the Darjeeling Himalaya. *Current science*, *89*(2), 264-268.

[18] Aniszewski, T. (2015). Alkaloids: Chemistry, Biology, Ecology, and Applications. Elsevier.

[19] György Matolcsy, Miklós Nádasy, Viktor Andriska Pesticide chemistry, Elsevier, 2002, pp. 21–22

[20] *Vinholes, Juliana; Coimbra, Manuel A.; Rocha, Sílvia M. (2009). "Rapid tool for assessment of C13 norisoprenoids in wines". Journal of Chromatography A.* ***1216*** *(47): 8398–403.*

[21] Martin, D. M., Gershenzon, J., & Bohlmann, J. (2003). Induction of volatile terpene biosynthesis and diurnal emission by methyl jasmonate in foliage of Norway spruce. *Plant physiology*, *132*(3), 1586-1599.

[22] Moyle, C. W., Cerezo, A. B., Winterbone, M. S., Hollands, W. J., Alexeev, Y., Needs, P. W., & Kroon, P. A. (2015). Potent inhibition of VEGFR-2 activation by tight binding of green tea epigallocatechin gallate and apple procyanidins to VEGF: Relevance to angiogenesis. *Molecular nutrition & food research*, *59*(3), 401-412.

[23] D'Archivio, M., Filesi, C., Varì, R., Scazzocchio, B., & Masella, R. (2010). Bioavailability of the polyphenols: status and controversies. *International Journal of Molecular Sciences*, *11*(4), 1321-1342.

[24] Pierson III, L. S., & Pierson, E. A. (2010). Metabolism and function of phenazines in bacteria: impacts on the behavior of bacteria in the environment and biotechnological processes. *Applied microbiology and biotechnology*, *86*(6), 1659-1670.

[25] Huffman, J., Gerber, R., & Du, L. (2010). Recent advancements in the biosynthetic mechanisms for polyketide-derived mycotoxins. *Biopolymers*, *93*(9), 764-776.

[26] Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative medicine and cellular longevity*, *2*(5), 270-278.

[27] Mattila, P., Hellström, J., & Törrönen, R. (2006). Phenolic acids in berries, fruits, and beverages. *Journal of agricultural and food chemistry*, *54*(19), 7193-7199.

[28] Mandal, S. M., Chakraborty, D., & Dey, S. (2010). Phenolic acids act as signaling molecules in plant-microbe symbioses. *Plant signaling & behavior*, *5*(4), 359-368.

[29] Huang, W. Y., Cai, Y. Z., & Zhang, Y. (2009). Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. *Nutrition and cancer*, *62*(1), 1-20.

[30] **30.** Rice-Evans, C. A., Miller, N. J., & Paganga, G. (1996). Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free radical biology and medicine*, *20*(7), 933-956.

[31] Ghasemzadeh, A., & Ghasemzadeh, N. (2011). Flavonoids and phenolic acids: Role and biochemical activity in plants and human. *Journal of medicinal plants research*, *5*(31), 6697-6703.

[32] Chiou, S., Lai, G., Lin, L., & Lin, G. (2006). Kinetics and mechanisms of cholesterol esterase inhibition by cardiovascular drugs in vitro. *INDIAN JOURNAL OF BIOCHEMISTRY AND BIOPHYSICS*, *43*(1), 52.

[33] Hardman, J. G., & Limbird, L. E. (2001). Goodman & gilman's the pharmacolog—iced basis of therapeutics.

[34] Adisakwattana, S., Intrawangso, J., Hemrid, A., Chanathong, B., & Mäkynen, K. (2012). Extracts of edible plants inhibit pancreatic lipase, cholesterol esterase and cholesterol micellization, and bind bile acids. *Food Technology and Biotechnology*, *50*(1), 11.

[35] Kumar, A. P., Sivashanmugam, A. T., Umamaheswari, M., Subhadradevi, V., & Jagannath, P. (2011). Cholesterol esterase enzyme inhibitory and antioxidant activities of leaves of Camellia sinensis (L.) Kuntze. using in vitro models. *International Journal of Pharmaceutical Sciences and Research*, *2*(10), 2675.