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Review Article

## Plant Secondary Metabolites of Antiviral Properties a Rich Medicinal Source for Drug Discovery: A Mini Review

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### ABSTRACT

Plants possess a unique defense mechanism unlike humans and animals that protects them from harmful microorganism to herbivores by secreting low molecular weight compounds called secondary metabolites. The compounds are concentrated in essential oil of the plants and its medicinal properties cure human illnesses too. Some of those plants still being used in traditional medicine by human, ever since civilized using plants as medicine. The ancient civilizations India, China and Europe only used plants as medicine. The emergence and enormous growth of allopathic medicine in the 19<sup>th</sup> century caused the downfall of the traditional medicine system. Now in the 21<sup>st</sup> century the scenario changed, the scientists trying to rediscover the ancient medicine through science to cure deadly diseases. In this review we focused on the researches that determined the antiviral properties of plant secondary metabolites for the development of drugs.

**Keywords:** Secondary metabolites, Antiviral properties, Alkaloids, Phenols, Viral diseases, Medicinal plants**Article Info:** Received 06 July 2019; Review Completed 19 August 2019; Accepted 22 August 2019; Available online 15 Sep 2019**Cite this article as:**Ebenezer KS, Manivannan R, Punniyamoorthy A, Tamilselvan C, Plant Secondary Metabolites of Antiviral Properties a Rich Medicinal Source for Drug Discovery: A Mini Review, Journal of Drug Delivery and Therapeutics. 2019; 9(5):161-167 <http://dx.doi.org/10.22270/jddt.v9i5.3471>**\*Address for Correspondence:**

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### Introduction

Plants produce large number of specialized small organic compounds called secondary metabolites, the natural products. Especially on genome of plant with more than 20,000-60,000 genes of which 15 to 20% encoded enzymes involved in secondary metabolism (Lattanzio, 2003). Secondary metabolites are often specific to a particular plant species because of their limited distribution in the plant kingdom (Dey, 2016 & Vincenzo Lattanzio *et al*, 2006), which also differs in concentration and types between the individuals of same population (Saurabh Pagare *et al*, 2015). Metabolites involved in plants defense mechanism either directly or indirectly to protect plants from insects through repellence, inducing toxicity and growth inhibition of competitive plants, from UV, attracting pollinating insects, seed dispersing animals and root nodule bacteria (Wink, 1999). Primary metabolites and their intermediates serve as precursors for secondary metabolites. Commercially used as dyes, flavors, drugs, insecticides and fragrances (Saurabh Pagare *et al*, 2015). Recent archeological study in China found a grinding stone with residues of medicinal plant's

millet, grains and roots the ancient people used to process, so hence secondary metabolites plays an important role in the novel drug discovery. This review gives an idea about the secondary metabolites involving in the antiviral activity.

### Discoveries of Secondary Metabolites

Globally, the researches on primary metabolites are peak, and either way the secondary consider as a waste product. On 19<sup>th</sup> century, the isolation of morphine by Friedrich Wilhelm Serturmer marked the research on plant secondary products (Hartmann, 2007). After, extensive research on secondary products, Kossel (1891) named these compounds as secondary metabolites since they are not involved in the plants primary metabolism, growth and development or reproduction (Ruby Tiwari and Rana 2015). Also he stated that it involve in plant's adaptation to the environment. It may also be consider for taxonomic markers because of their limited distribution in the taxonomy. After the discovery, the next 150 years attributed on isolation of compounds, to determine its structure and category. Hartmann (2007) proposed a theory, that the secondary metabolite product

used for evolutionary development in the plants for its adaptation to the environmental conditions. Today, it extensively used commercially in pharmaceuticals, cosmetics, textiles, as recreational drugs etc. Recently, focus of modern research mainly on genetic level of the metabolites. So in future it may create a revolution for discovery of different metabolic pathways and biological values towards drugs.

### Important Classification in Secondary Metabolites

Ruby Tiwari and Rana (2015) classified the secondary metabolites into three types as terpenes, alkaloids and phenolics. The terpenoids widely spread out and largest group with more than 40,000 structures (Gershenzon *et al.*, 2007). They are polymeric molecules made of isoprene units ( $C_5H_8$ ) synthesized by mevalonic acid pathway (Justin *et al.*, 2014).

Many researchers reported that terpenoids are derived from the universal five-carbon building blocks, isopentenyl diphosphate (IPP) and its allylic isomer dimethylallyl diphosphate (DMAPP) which are synthesized from acetate. Tholl (2015) reported that condensation of above mentioned five carbon molecule produces prenyl diphosphate intermediates, precursors for biosynthesis of terpenoids. The terpenes play a crucial role as both primary and secondary metabolite; classified based on their isoprene units into mono, di, sesqui terpenes (Gershenzon *et al.*, 2007). But the major classification includes the following as hemiterpenes with one isoprene unit, monoterpenes with two isoprene units which is further classified based on the structural form, sesquiterpenes with three isoprene units, diterpenes with four isoprene units, sesterpenes with five isoprene units, triterpenes with six isoprene units and tetraterpenes containing eight isoprene units. The group with more than eight units of isoprene is called polyterpenes. Rubber is an example of terpenes. Other commercially used terpenoids are menthol, hormones, carotenoids and essential oils (Mathilde, *et al.*, 2016).

Alkaloids are toxic compounds that protect plants against infections and commercially used as medicine, biosynthesized from amino acids like tyrosine (Evans *et al.*, 1982). According to Ruiz and Sotelo (2001) reported alkaloids synthesized from both aromatic and aliphatic amino acids like tyrosine, lysin, tryptophan and aspartic acid by either pyruvate pathway or shikimic acid pathway. About 10,000 alkaloid compounds isolated so far reported by Mathilde, *et al.*, 2016. The structure contains crystalline substances with a free state N-oxide. Of the three, alkaloids are structurally most diverse group. Thus, in earlier time they are poorly classified based on the plant they belong, since the structural composition was not fully understood. Now, the development in modern chemistry has led to the classification into three groups based on the structure (Evans, 2009) such as alkaloids with nitrogen atom and a heterocyclic ring structured derived from amino acids and contains about 14 groups. Steroids, quinolines are among them; Amines with non- heterocyclic rings; Steroidal alkaloids with heterocyclic ring containing nitrogen atom but derived from substances other than amino acids (Ahmad *et al.*, 2017).

Phenolics are highly diverse group of all three metabolites and present in almost all the plants (Pengelly, 2004). With one or more functional hydroxyl group on a benzene ring (Velderrain-oderiguez *et al.*, 2014). Likely monomer, dimer and polymer structures based on their structure the phenols are classified in to simple phenols, benzoquinones ( $C_6$ ); phenolic acid ( $C_6-C_1$ ); phenylacetic acid, acetophenone ( $C_6-C_2$ ); hydroxycinnamic acids, coumarins, phenylpropanes, chromones ( $C_6-C_3$ ); naphthoquinones ( $C_6-C_4$ ); Xanthenes ( $C_6-C_1-C_6$ ); stibenes, anthraquinones ( $C_6-C_2-C_6$ ); flavonoids, isoflavonoids ( $C_6-C_3-C_6$ ); lignans, neolignans ( $C_6-C_3$ ); biflavonoids ( $C_6-C_3-C_6$ ); lignins ( $C_6-C_3$ )<sub>n</sub>; catechol melanins ( $C_6$ )<sub>n</sub>; condensed tannins ( $C_6-C_3-C_6$ )<sub>n</sub> (Harborne, J.B. 1980). These compounds are synthesized by the combination of pentose phosphate pathway, glycolysis and shikimate pathway in plants (Lin *et al.*, 2010).

### Role of Secondary Metabolites in Plant Defense

Most of the terpenes are secondary metabolites but some also take part in primary metabolism, for example Gibberellin a diterpene act as toxins and feeding deterrents. In *Chrysanthemum* species, a monoterpene called pyrethroid acts as the insecticidal agent, commercially used in pesticides. The role of terpenes extensively studied in conifer species. Conifers contains only about 600 species but spread throughout the world and ecologically significant (Mumm and Hilker 2006; Nystedt *et al.* 2013). These trees contain large amount of terpenes in their tissues occurs in the form of a mixture called oleoresin contained in resin ducts. The oleoresin mixture consists of two fractions: turpentine and rosin. During attack of insects or physical damage, the turpentine fraction acts as insecticidal/fungicidal and readily evaporates then the rosin fraction hardens cover the wound, also trap the insect within the mixture (Phillips and Croteau, 1999; Trapp and Croteau, 2001). Mostly the terpenes in plants as essential oil having antibacterial, antiviral, antioxidant properties, also protects plants by attracting or deterring insects (Bakkali *et al.*, 2008).

Alkaloids are known for many pharmacological effects on vertebrates and used since ancient times in the protection of the cultured crops. The toxic mechanism of various class of alkaloid is different as well as its pathological effects on insects. The pathological effects include endosymbiosis, retardation of growth and development, inhibition of respiration, inhibiting nervous system and mortality (Yang and Stockigt 2010). The secondary metabolites mainly alkaloids detected using the advance techniques liquid chromatography coupled to nuclear magnetic resonance (LC-NMR) and some alkaloids in plants with medicinal properties (Triston *et al.*, 2013) (Figure 1).

The role of phenols in plants includes antibacterial, anti-nutritional and acts as pigment, metal chelators, signaling compounds and UV screen lights. All comprises of aromatic ring and phenolic group bounded with each other. Some simple group phenols such as p-hydroxybenzoic acid, vanillic acid, syringic acid, coumaric acid and cinnamic acid (Kamila kulbat, 2016) (Figure 2).

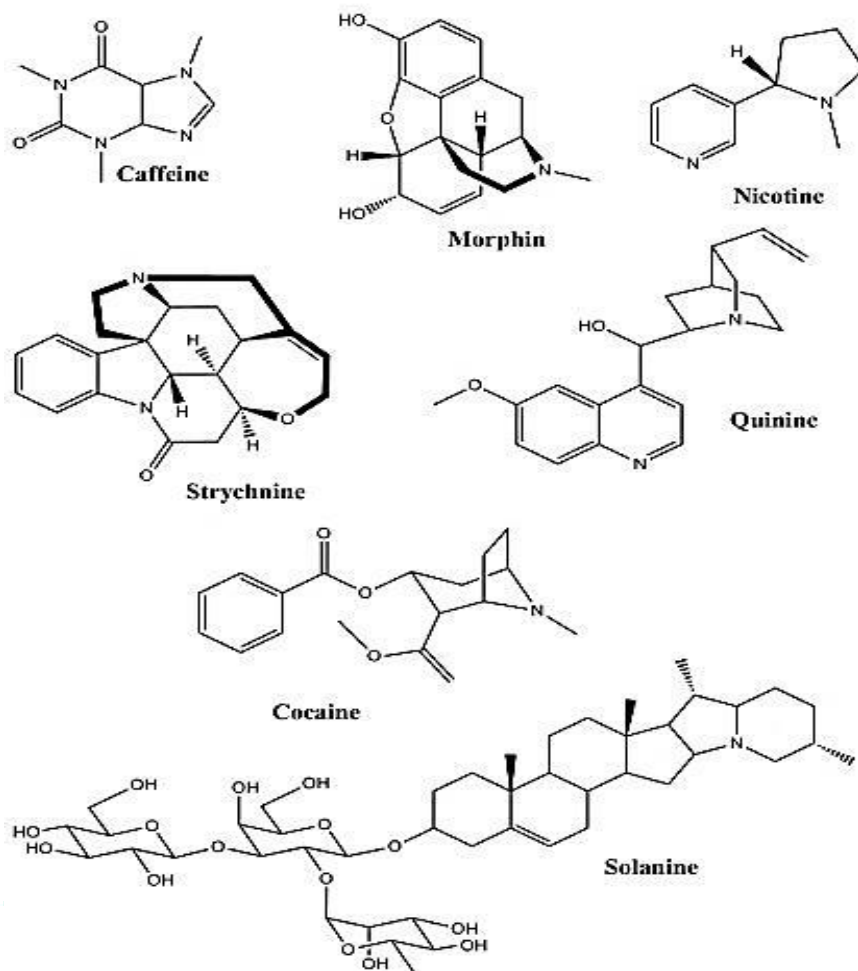


Figure 1: Alkaloids in different plants (Triston *et al*, 2013)

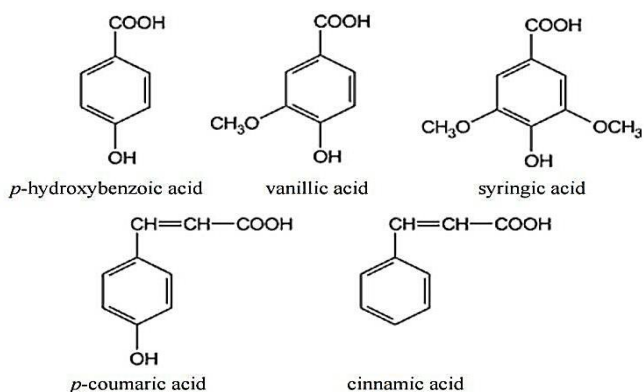


Figure 2: Phenols in plants (Kamila Kulbat, 2016)

### Antiviral Properties of Secondary Metabolites in Medicinal Plants

#### Terpenes

Monoterpenes, the common class of terpenes. Akram Astani *et al*, (2009) reported that different monoterpenes with antiviral properties,  $\alpha$ -terpinene,  $\gamma$ -terpinene,  $\alpha$ -pinene, *p*-cymene, terpinen-4-ol,  $\alpha$ -terpineol, thymol, citral and 1,8-

cineolepentacyclic triterpenoid in essential oils from eucalyptus, thyme, and tea tree against herpes simplex virus type 1 (HSV-1). *In vitro*, the monoterpenes in oil showed 80% inhibition of HSV-1. In natural tea, monoterpenes as a mixture of tenfold highest selectivity index against the virus than the individual compounds. Examples of some essentials in the plants having activity towards the medicinal properties (Bayala *et al*, 2014) (Figure 3).

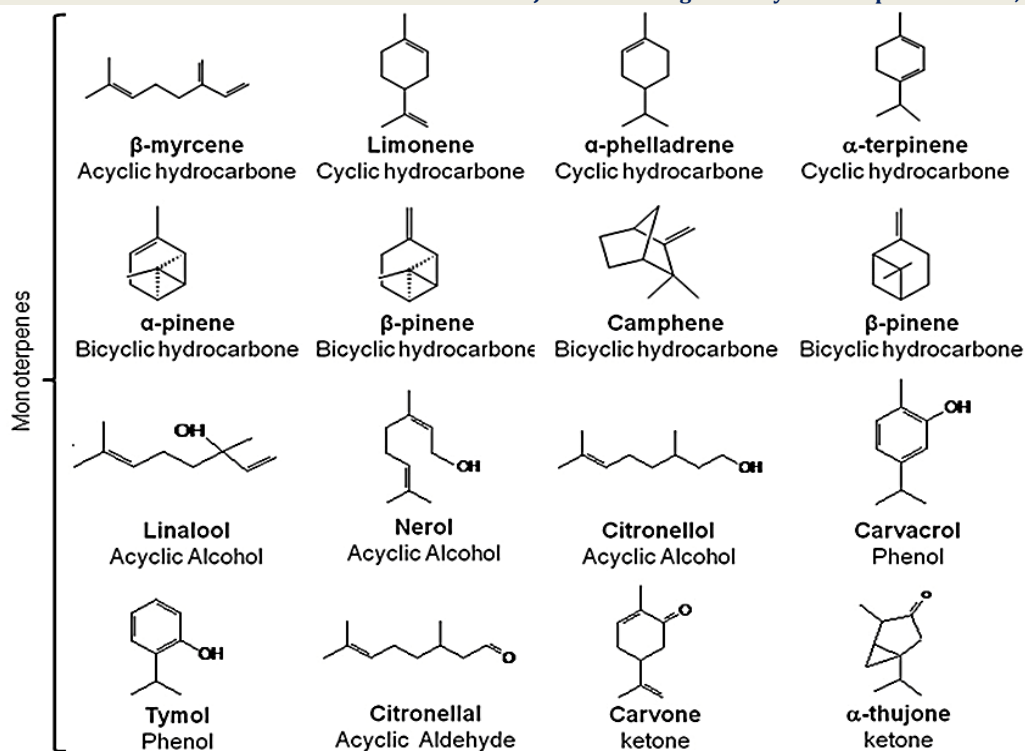


Figure 3: Some examples of monoterpenes essential oils of various plants (Bayala *et al*, 2014).

The essential oils blend of *Eucalyptus globulus*, *Cinnamomum zeylanicum*, *Daucus carota* and *Rosmarinus officinalis* proved anti-H1N1 and anti-HSV1 properties. The essential oils reduced the viral count significantly at different concentrations (Brochot A *et al*, 2017). Another report stated that anti-dengue activity of nine synthetically derived compounds tested in essential oils (Maria *et al*, 2018). Four genetically related serotypes of dengue virus i.e. DENV-1, DENV-2, DENV-3 and DENV-4 is the cause of the dengue disease (Mukhopadhyay *et al*, 2005). Of the nine compounds tested,  $\beta$ - Caryophyllene, a bicyclic sesquiterpene inhibited all four serotypes with less inhibitory concentration (IC<sub>50</sub>: 16  $\mu$ M) and highly effective during the early steps of the

virus life cycle. The citral showed inhibitory effect against DENV-2 serotype (Flechas *et al*, 2018) and  $\beta$ - Caryophyllene appeared in black pepper, cloves, cinnamon and cannabis (Orav, A *et al*, 2005). Crocin, a carotenoid compound of saffron, in an attempt to find a novel drug with less side effects and toxicity, crocin from saffron was found as anti-HSV-1 and anti-HIV-1 in vero cells infected with the viruses. The compound showed significant effect by both inhibition of HSV entry into the cells and disrupting virus replication inside the cells. But the aqueous saffron extract unable to inhibit or lesser inhibition of the viruses (Sepehr *et al*, 2017) (Figure 4).

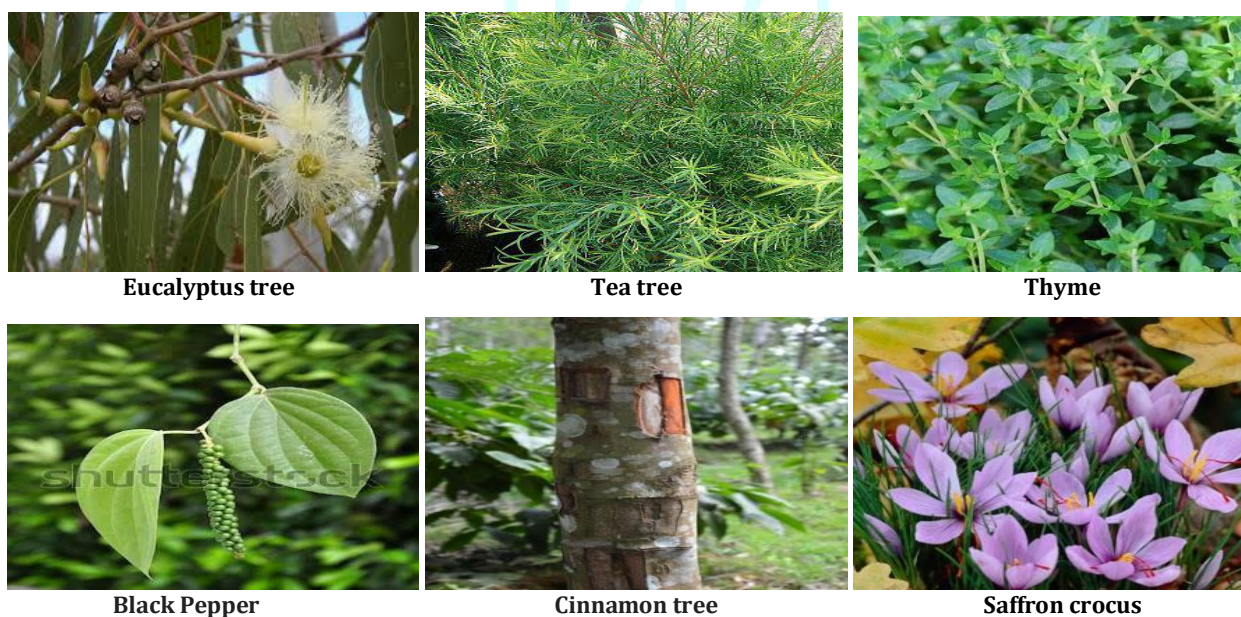


Figure 4: Plant source for essential oils

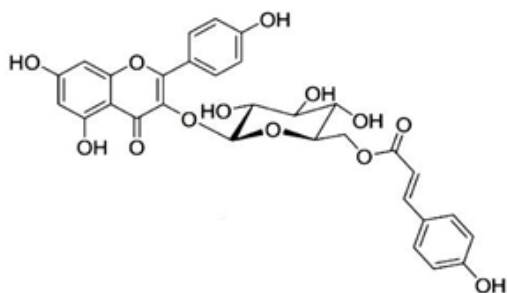
## Phenolics Compounds of Secondary Metabolites

Phenolic compounds predominantly in fruits, vegetables, most legumes and food grains, seeds, stems, leaves, flowers, roots and barks as well as tea, red wine, chocolate and honey is the main constituent of human diet (Constantine 2007). Among the major classes, polyphenols and flavonoids have antiviral properties against HIV, HSV, dengue virus, influenza virus and polio virus (Anjoo Kamboj, 2012). Nowadays, many plants under research to evaluate the contents of phenols and their antiviral properties. *Euphorbia spindens* of Euphorbiaceae tested for total phenolic content and activity against HSV. The total phenolic and flavonoid

contents were  $70 \pm 1$  mg GAE/g extract and  $49.66 \pm 0.996$  mg RTN/g extract respectively. Time course analysis of antiviral activity at different concentrations showed that the highest inhibition was seen at 5mg/ml concentration within 2 hours after virus infection (Ali Karimi *et al*, 2016). *Bombax malabaricum* flowers, native to China is used as a healthy food material and flowers were tested and three new phenolic compounds were detected. All isolated compounds evaluated for anti-RSV activities in CPE reduction assay and confirmed by plaque reduction assay. Kaempferol-3-O-(6''-O-E-p-coumaroyl)- $\beta$ -D-glucopyranoside one of three new compound has similar activity like ribavirin drug (Yu-Bo Zhang *et al*, 2015) (Figure 5 & 6).

a. *Euphorbia spindens**Bombax malabaricum* tree and flowers

Figure 5: Phenolic compound source from medicinal plants

Figure 6: Kaempferol-3-O-(6''-O-E-p-coumaroyl)- $\beta$ -D-glucopyranoside

Another widely used plant species *Mentha piperita* L. (Peppermint) tested for its antiviral activities. The total phenolic and flavonoid contents found to be  $325.84 \pm 14.17$   $\mu$ g/mg gallic acid and ethanol extract of the plant showed potent *in vitro* anti-RSV activity in Hep-2 cells which act as a promising drug in future (YuXian Li *et al*, 2017). China and India are the world leading producers and Turkey is the world leading consumers of black tea (*Camellia sinensis*). The hydroalcoholic extract of black tea inhibited adenovirus (ADV) replication in post adsorption stage with a selectivity index of 25.06. Antiviral activity attributed to the total phenol and flavonoid contents in plant found to be  $341.8 \pm 4.41$  mg gallic acid equivalent per gram and  $21.1 \pm 2.11$  mg/g, respectively (Ali karmi *et al*, 2016) (Figure 7).

*Mentha piperita* L.*Camellia sinensis*

Figure 7: Medicinal plants for Adenovirus inhibition

## Alkaloids

Many plant derived alkaloids used for medicinal purposes from the ancient period. Quinine is one such alkaloid in the bark of the tropical cinchona tree used for fever. In 17<sup>th</sup> century, the researchers found that antimalarial activity in bark and later the compound quinine purified in 19<sup>th</sup>

century and treated for malaria disease instead of the crude bark extract. Similarly, The vincleukoblastine and vincristine used for white blood cell cancer treatment, atropine from several plants to treat insecticide poisoning, as a nerve agent.

*Peganum harmala* L. perennial glabrous plant grows in India, South America, Middle East, Africa, China and in most

parts of Iran used as a herbal medicine. The extract of the plant contains beta-carbolines (harmine, harmaline, harman and harmalol) and quinazoline derivatives of vasicine and vasicinone alkaloids (Mina *et al*, 2015). The study on seed extract of the plant showed that antiviral activity of total alkaloids (beta-carbolines) significantly greater than that of crude extract with a selectivity index of 23.1 against influenza virus (Mohammad-Taghi *et al*, 2017). Still now, there is no drugs for Human cytomegalovirus (HCMV) a widespread disease causing mortality in immunocompromised patients only antiviral medication

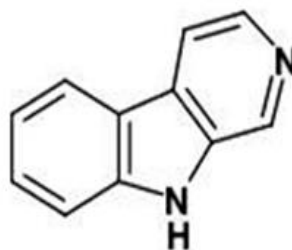


Figure 8: *Peganum harmala L.* and Beta carboline alkaloid against influenza virus

## Conclusion

When humans started to live in closed agricultural communities, infectious diseases mainly the viral diseases started to infect (McMichael AJ, 2004). Globally, throughout the history large outbreaks of viral diseases caused higher mortality rates. Even in 21<sup>st</sup> century outbreaks of new viral diseases like Ebola virus and Nipah virus caused higher mortality rates within a short period. Also the previous viral strains becoming resistant to the drugs. Hence, medicinal field of research is needed to find novel drugs.

With the development of science and technology, researches being conducted worldwide with the aim to discover drugs from plants. The herbal medicinal system always an alternative for allopathic medicinal system, the plant secondary metabolites with antibacterial, antiviral, antioxidant and other certain medicinal properties in nature. Compared to allopathic medicine, the plant derived compounds possess less cytotoxicity to humans and higher inhibition rate of viruses which creating great interest among researchers. Most of the researches conducted on plants in order to discover the compounds responsible for their medicinal properties that long since used in folk medicine. Here we discussed the secondary metabolites with antiviral properties and future key for the development of novel drugs from those identified compounds for the eradication of viral diseases.

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