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How to Cope with Dengue in Developing Countries Like Pakistan?

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ABSTRACT

A viral disease like dengue lacking a specific form of treatment is a high menace to human health. Situation becomes worse in developing countries like Pakistan because of poor health care services and facilities. Using data from earlier works and analyzing them, this review aims to explore the disease epidemiology. Dengue Virus (DENV) destroys the immune system and causes health problems like headache, inflammation, bleeding, hypertension and mental disorders. Death also can be caused through dengue because of its adverse effects on liver which also may result in hepatitis. Dengue spread can be controlled through many ways like modulating the environment and devastating its vector. Biological control appears as potential approach to control its vector, especially the use of *Wolbachia*. Currently, no vaccines are available against this virus and antiviral drugs are also not significantly effective. Phytochemical studies revealed that apple, papaya and lemon are rich source of carotenoids, esters, flavonoids, phenolic acid, terpene and vitamins. Apple was found to have a number of antiviral compounds like phytoestrogens, procyanidins and rosmarinic acid. Although there are few reports of antiviral compound obtained from papaya but it has been reported to have evocative beneficial effects on immune system. The phytochemicals behave as strong anti-oxidant and anti-inflammatory agents which can help the body against dengue-induced inflammation and oxidation stresses. Several other features are also found in these reviewed phytochemicals that can protects the human body from the adverse effects of dengue infection. In nutshell, the consuming of papaya and apple should be incorporated in daily routine life especially during the season when this disease appears in its epidemic form.

Key words: *Aedes aegypti*, $CD8^+$, $CD4^+$, anti-oxidant, anti-inflammatory, platelet, hepatitis, secondary complications, *Wolbachia*

INTRODUCTION

During last ten years, the total number of dengue patients has been doubled (Bigongiari, 2010). WHO (World Health Organization) in 2010 also reported a graver concern is that about 100 million cases of dengue are not administrated by medical staff and 0.5-2.5% of these suffers with severe harmful consequences of virus (Deen *et al*., 2006). Dengue is a vector born virus and has four different types DENV-1, DENV-2, DENV-3 and DENV-4 called serotypes (Jahan, 2011). Its four serotypes originated approximately 1000 years ago and from past few hundred years, it starts infecting humans (Holmes and Twiddy, 2003). Dengue has large distribution due to its low

entomological threshold level and it is mainly transmitted by the biting of infected *Aedes aegypti* and *Stegomyia albopicta* (Scott and Morrison, 2010; Cecilio *et al*., 2009). Many other dengue transmitting vectors are also known but several studies on *A. aegypti* describes its major significant role in transmitting the virus (Anderson and Rico-Hesse, 2006; El-Badry and Al-Ali, 2010; Focks *et al*., 2000; Harrington *et al*., 2005; Mohammed *et al*., 2008; Phongsamart *et al*., 2008). *A. aegypti* extensively favors the dengue dispersal due to its diverse distribution in phytotelmata and peridomestic environments like earthen pots, containers, tyres etc. (Adebote *et al*., 2006; Adebote *et al*., 2008; Bashar *et al*., 2005).

In Pakistan, Dengue may be observed throughout the year but high dengue inflectional period is from October to December (Khan *et al*., 2010; Tahir *et al*., 2010). According to a report on tertiary care hospital, in Pakistan large number of dengue infections is mostly detected during winter season (Wasay *et al*., 2008). Pakistan is one of the developing nations where approximately, one fourth of its population lives below the line of poverty (The World Bank). It is thus basic health care facilities are not readily available for most of the people resulting use of alternate medicines is a much common phenomenon (Qureshi *et al*., 2001; Khan *et al*., 2003; Karim *et al*., 2011; Sohail *et al*., 2011). Since last couple of years, dengue has emerged as an epidemic disease and use of papaya, apple and lemon extracts to treat dengue fever was found to be very common. But, there are not much scientific studies available to support the use of these extracts for the treatment of this disease. So literature was reviewed to find the potential beneficial activity of these plants against dengue on the basis of their reported phytochemicals. In addition a brief look at disease symptoms and approaches to control it has been provided under the lights of previous studies.

EFFECTS ON HUMAN BODY

Symptoms caused by dengue may be in overlap with other diseases. These symptoms are fever, headache, nausea, skin rash and ocular pain (Ali *et al*., 2011; Humayoun *et al*., 2010). Dengue patients suffer from gastrointestinal bleeding, headache and several neurological problems. It is also observed that 100% of the dengue patients have significantly lower values of platelets in their body while the lower number of neutrophils and leukocyte were also recorded in 58 and 88% of the patients, respectively (Hakim *et al*., 2011). Dengue also disturbs the liver by increasing the concentrations of alanine transaminase (ALT) and aspartate transaminase (AST), liver enzymes. There are chances of mild-severe hepatitis on infection with dengue, which increases the complications like gastrointestinal bleeding, hypertension, mental disorders and inflammation of gall bladder and ultimately leads to the death of patients (Almas *et al*., 2010; Parkash *et al*., 2010; Souza *et al*., 2008). Dengue also affects the muscle cells by causing inflammation, which may be due to the increased intracellular Ca^{2+} concentrations (Salgado *et al*., 2010). The development of disease symptoms directly correlates with the presence of IgM antigen of dengue (Tang *et al*., 2008). While the presence of viral RNA does not play any role in dengue caused symptoms, the disease severity could increase if patient again come into contact with different serotype of dengue virus (Sierra *et al*., 2010). This severity may be due to increased imbalance in immune system regulation. The dengue virus also harms its mosquito vector; it cause apoptosis in mosquito tissues during its life cycle (Shafee and AbuBakar, 2006a). The observed apoptosis was not the part of metamorphic programmed cell death as the apoptosis was directly proportional to the number of virus antigen positive cells.

HUMAN IMMUNE RESPONSES TO VIRUS

Today's vulnerable environmental and poor human health conditions make the global spread of dengue rapidly (Guzman and Isturiz, 2010). Therefore, the understanding of significant features of human immune system in relation to viral attacks may help to reduce the severity of this disease. The human immune system is of two types called innate and adaptive immune system (Cooper and Herrin, 2010; Smith and Weyrich, 2010). The immunity against pathogen and injury is governed by both innate (e.g., through platelets) and induced (through a variety of lymphocytes e.g., T and B cells) immune systems. The T and B cells have antigen recognizing complex to identify the harming pathogens. On the other hand, platelets stabilize the disturbed homeostasis and translocate the information among immunity responsive T, B and neural cells (Varga-Szabo *et al*., 2008; Wannemacher *et al*., 2011). Monocytes (type of white blood cells) are the source of innate and adaptive immunity responses (Auffray *et al*., 2009; Serbina *et al*., 2008). As they take part in the development process of dendritic cells and macrophages, healing and clearance of pathogens. Moreover, these are also an important tool against DENV (Klomporn *et al*., 2010). Any pathogen like virus affects the various immune responses; it targets the antigen identification complex, apoptosis and hormonal immune responses (Tortorella *et al*., 2008). Virus causes the abnormality in the function of B cells, which may be due to some kinds of association developed between virus and B cells (Stamataki *et al*., 2009). $CD4^+$ (primary immune response) and $CD8^+$ (secondary immune response) are the types of T cells and stop the invasion of virus (Jiang and Chess, 2004; Strowig *et al*., 2009) and number of these cells indicates the severity of disease (Ahasan *et al*., 2004; Kagone *et al*., 2011). The absence of these T cells in body can negatively increase viral-mediated diseases, as was observed in mouse infected with Epstein-Barr virus. The dengue virus receives more prevalent situation in mice depleted with $CD8^+$ T cells while $CD4^+$ T cells depletion didn't show any kind of effect (Yauch *et al*., 2009; Yauch *et al*., 2010). But the T and B cells are not the major inhibitors of virus particles instead macrophages play major role in the inhibition of virus (Blackley *et al*., 2007; Kou *et al*., 2008). Thus for a successful infection virus has to kill the macrophages but the T and B cells do have some antiviral effects.

Upon viral infection the $CD8^+$ T cells enhanced the expression of Programmed Death 1 (PD1) responses with the help of $CD4^+$ T cells (Barber *et al*., 2006; Petrovas *et al*., 2006). Virus triggers the expression of T regulatory cells ($CD4^+CD25^+$ T cells) and these cells suppress the proliferation of virus specific $CD4^+$ T and $CD8^+$ T immune cells (Boettler *et al*., 2005; Weiss *et al*., 2004). Thus $CD4^+CD25^+$ T cells are responsible for the pathogenic effects of virus in the body but its activity may be suppressed over time as observed in HCV recovered patients (Pearson *et al*., 2008). The platelet can destruct the virus by engulfing it (Torre and Pugliese, 2008; Youssefian *et al*., 2002). But if virus bound with platelet through specific ligands, it may alter the platelet's activity (Flaujac *et al*., 2010). The altered platelets activity can disseminate the virus within the body as Hantavirus causes the change in the platelets activity to favor its dissemination (Gavrilovskaya *et al*., 2010). Nitric oxide concentration plays a significant role in different body functions (Najati *et al*., 2008; Moazedi *et al*., 2010). Dengue virus elevates the nitric oxide (NO) levels, which inhibit the adhesion of platelets and cause bleeding (Mendes-Ribeiro *et al*., 2008). NO toxicity may be the main reason of dengue caused health problems (Chaturvedi and Nagar, 2009). Some dengue proteins e.g. Non-Structural Protein 1 (NS1) are homologue of coagulatory proteins (Lin *et al*., 2011). The resultant antibody produced against these viral proteins cross react with coagulatory proteins and damage the platelets. The homologue responsible portion of NS1 is the C-terminal and if C-terminal is removed, this viral protein would be unable in affecting the

platelets (Chen *et al*., 2009). The antibodies produced against NS1 also cause severe damages to liver, which may be due the elevated levels of AST and ALT enzymes (Lin *et al*., 2008a). The infection of dengue can be minimized by strengthening the immune responses.

As DENV does not affect the single cell type or organ of the body, it can be concluded that dengue has complex mechanisms of action. This may also be due to the reason that its infection in one type of cell can severely effects whole body health. For example, the T cells, which recognize any antigen of pathogen upon dengue-caused reduction, would be unable to recognize other antigens. Likewise, dengue caused reduction in platelets not only affects the coagulatory responses but also results in reduce signaling between other immune cell. Thus, there is not only the need to reduce the dengue infections but also to treat the other complications that originate as consequences of this disease.

CONTROL OF DENGUE

Viral diseases such as rabies, herpes, influenza, hepatitis and HIV have always remained as important discourse amongst health scientists in order to have better understanding of these diseases (Farooq *et al*., 2006; Oguntibeju *et al*., 2007; Ilboudo *et al*., 2009; Movahed and Shoaa, 2010; Shabahang, 2010; Hassanzadeh *et al*., 2011). Studies based on the prevalence of these diseases helps to identify the geological distribution and factors responsible for their spread (Moghim *et al*., 2007; Ilboudo *et al*., 2007; Talaie *et al*., 2007; Daryani *et al*., 2009; Sagna *et al*., 2010). The non-preventive measures for urbanization, globalization, modern air transport, water and waste management cause the rapid infestation of environment with dengue and its vector (Barboza *et al*., 2008; Gubler, 2010; Kyle and Harris, 2008; Ooi and Gubler, 2008; Ooi and Gubler, 2009). This huge spread of dengue can be minimized by modulating our environment like managing the cool air supply in the houses, use of insecticide treated materials and frequent distance from neighboring houses (Reiter *et al*., 2003; Vanlerberghe *et al*., 2011). There are two fundamental types of controls. They are (1) "before infection" and (2) "after infection" (Fig. 1). "Before infection control" is based on preventive measures to avoid disease e.g., vector control and vaccination. "After infection control" consists of efforts that are focused on suppression of virus attack and its related complications.

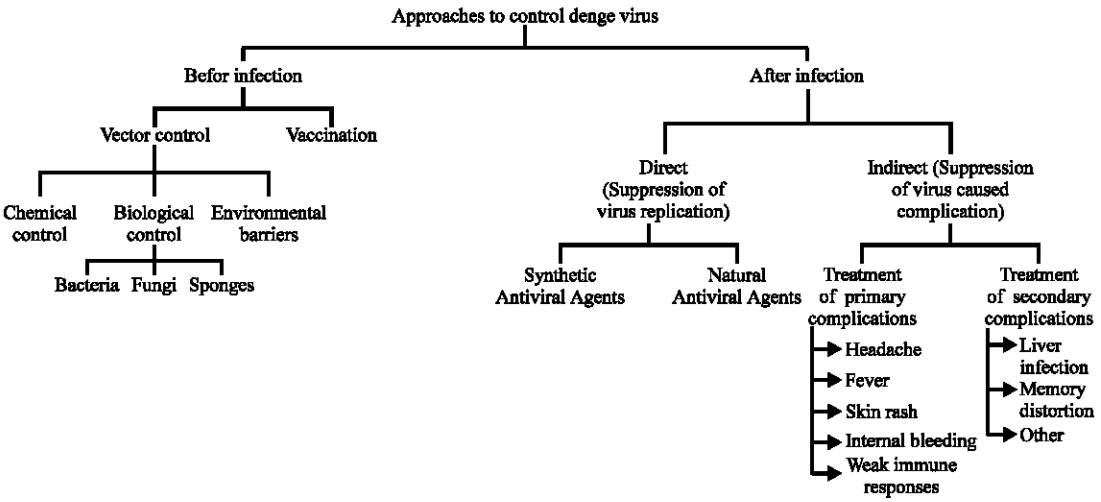

Fig. 1: A schematic diagram describing the general layout of dengue disease management

REDUCED DISSEMINATION OF VIRUS

The best way to control a virus is to control its vector; *A. aegypti* is the main vector of dengue virus and control of this vector will definitely result in the reduced spread of this disease. Thus, the spread of dengue can be controlled by elimination of its vector *A. aegypti*; many studies have been conducted in this regard (Morrison *et al*., 2008; Paulraj *et al*., 2011; Raghavendra *et al*., 2011). The control of *A. aegypti* is necessary as it also causes another important lethal disease, malaria (Yasinzai and Kakarsulemankhel, 2003). Synthetic insecticides are not much effective against *A. aegypti* population as many of its strains have obtained the resistance against the commonly used insecticide and insects are only susceptible to the insecticide at specific life stage (Ahmad *et al*., 2007; Ocampo *et al*., 2011). Moreover, the use of these synthetic insecticides is also harmful for environment and causes stern health issues (Al-Jahdali and Bisher, 2007). So environment friendly and effective method like biological control of *A. aegypti* appears as more suitable approach. There are many approaches to biologically control the virus's vector e.g. *Bacillus thuringiensis israelensis* (Alam *et al*., 2008). Its 'Cry' proteins have potential to control *A. aegypti* but these are sensitive to heat; heat suppresses the proteins' activity. The marine environment also offers biological control against this mosquito species in the form of sponges like *Clathria gorgonoids, Callyspongia diffusa, Haliclona pigmentifera, Sigmadocia carnosa* etc. (Sujatha and Joseph, 2011). Among these *C. gorgonoids* and *C. diffusa* showed the significant larvicidal activity at V instar larvae stage. The marine algae also showed larvicidal activity against *A. aegypti* (Manilal *et al*., 2011). The potentially important larvicidal activity was found in *Lobophora variegata*. Another important biological control of *A. aegypti* is *Wolbachia*. It causes alternations in host reproductive organs and modulates the host genomic expression to confirm its establishment in the host body (Hussain *et al*., 2011; Saridaki and Bourtzis, 2010). The *Wolbachia* strains cause viral transmission reducing phenomenon in mosquito like shortened life-span and cytoplasmic incompatibility (McMeniman *et al*., 2009; Yeap *et al*., 2010). It also lessened the feeding success of mosquito on human body which may be due to the tissue damage caused by *Wolbachia* (Moreira *et al*., 2009a; Turley *et al*., 2009). Less feeding eventually result in less transmission of virus. The potential of *Wolbachia* to infect the mosquito depends upon the *Wolbachia* strain type; establishment of genetically different *Wolbachia* strains may cause more promising effects (Walker *et al*., 2011; Xi *et al*., 2005).

The spread of dengue can also be limited by the use of nanoparticles. The nanoparticles of silver upon exposure to UV radiations show the efficient ability to kill *A. aegypti* larvae, in a concentration dependant manner (Sap-Iam *et al*., 2010). The virus transmission can also be controlled, if the immune system of *A. aegypti* is strong enough to reject the virus infection (Sanchez-Vargas *et al*., 2009; Xi *et al*., 2008). Ahmed *et al*. (2008) observed that the application of *Nigella sativa* derived thymoquinone strengthen the immune responses of *A. aegypti*. In later studies it was observed that *Wolbachia* can provide strength to anti-dengue immune responses of *A. aegypti* (Bian *et al*., 2010; Frentiu *et al*., 2010; Moreira *et al*., 2009b). It enhances the expression of immune genes of *A. aegypti* against dengue infection and it strongly reduces the number of virus particles in the mosquito tissues. Among all the vector control methods, *Wolbachia* mediated biological control appears to be the prominent option.

VACCINES FOR DENGUE

Dengue has different mechanism of actions depending upon the type of cell line and in humans the immunity responses are highly dependent on their genetic polymorphism (Chaturvedi *et al*.,

2006; Shafee and AbuBakar, 2011). Today's approach is to obtain anti-dengue vaccines but these vaccines are still under development due to their adverse effects and short-lived immunity responses (Guirakhoo *et al*., 2006; Kanesa-Thasan *et al*., 2001; Guzman *et al*., 2010; Murphy and Whitehead, 2011). The virus particles based vaccine can be used to develop the immunity against dengue (Mota *et al*., 2005; Shafee and AbuBakar, 2006b). Tambunan and Parikesit (2011) provide the *in silico* design of E DENV vaccines for dengue-2 and 3, E DENV are the virus proteins which facilitate the attachment of virus on the host cell. But the functionality of these vaccines also depends upon the genetic system of human being so there is need of more computational power to fully express the efficiency and establishment of these vaccines. The intramuscularly applied plasmid of DEN-2 non-structural protein 1 (NS1) in mice causes decrease in morbidity and ultimately leads to the increased chances of survival (Wu *et al*., 2003). The immunity in the newborn of this NS1-treated mouse was more pronounced. But the increasing demand of DNA derived vaccines has increased the need of large quantities of pure DNA plasmid and the extraction of DNA plasmid is an important and difficult procedure (Duarte *et al*., 2007; Li *et al*., 2008a). Moreira *et al*. (2007) found the PEG 400 (20/20% w/w) system as the best PEG/phosphate system for the extraction of dengue 2 plasmid DNA vaccines from the lysate cells of *E. coli*. It can extract 37% of DNA plasmid. Thus this can be concluded that the development of vaccines to cure dengue has many limitations and there is need of more research on their efficiency and production.

ANTIVIRAL AGENTS

In nature many compounds are present that can be employed against viral diseases (Baranisrinivasan *et al*., 2009; Momtaz and Abdollahi, 2010; Vignesh *et al*., 2011). Squalamine, a compound obtained from dogfish shark and sea lamprey has the potent antiviral activity against many viruses including dengue (Zasloff *et al*., 2011). *In vitro* it has concentration dependent protective effects on human endothelial cells against dengue. Nearly thirty seven licensed antiviral drugs are present today, yet no reliable anti-dengue drug is present (De Clercq, 2004; Czeizel *et al*., 2006). But, dengue proliferation can be controlled by targeting the vulnerable sites of dengue life cycle using the small drug molecules (Wilder-Smith *et al*., 2010). According to Schul *et al*. (2007) the use of antiviral drugs even after acute dengue infection can significantly cause the reduction in virus particles and virus-caused disease. They further proposed that AG129 mice model is an appropriate object to study the anti-dengue drugs. Another chemical compound NITD008, which is the analogue of adenosine, also showed the potential antiviral activity against many vector-borne viruses especially dengue (Yin *et al*., 2009). It shows the dengue virus titer and virus-caused disease reducing ability in both *in vitro* and *in vivo* studies. But the significance of any anti-dengue drug is needed to check in human trials. Moreover the antiviral drug should also be checked on the basis of its origin, cost, cytotoxicity, purification etc. (Selisko *et al*., 2007). As many natural anti-dengue drugs derived from plants were rejected in past due to their difficult extraction and cytotoxic effects. Thus the development of anti-dengue drugs has many hurdles, but their development should be checked on critical basis.

PHYTOCHEMICAL STUDY OF APPLE, LEMON AND PAPAYA FOR THE TREATMENT OF DENGUE FEVER AND ITS RELATED COMPLICATIONS

The daily intake of 400-600 g of fruits and vegetables prevents from many diseases (Heber, 2004). The phytochemicals found in these plants have many therapeutic effects on human body (Garba *et al*., 2006; Musa *et al*., 2008; Yang *et al*., 2008a; Prakash and Gupta, 2009;

Table 1: Some reported phytochemicals of apple, lemon and papaya

Chemical class	Phytochemicals name	Reference
Phytochemicals of Apple		
Flavonoids	Procyanidins, Quercetin and its Derivatives, Catechin, Phloretin glycosides and Rutin	Boyer and Liu (2004), Ceymann *et al.*(2011), Gerhauser (2008), He and Liu (2008); Hossain *et al.* (2009), Marks *et al.* (2007), Sultana and Anwar (2008), Vanzani *et al.* (2005) Wach *et al.* (2007)
Vitamin	Ascorbic acid	Li *et al.* (2008b), Vanzani *et al.* (2005)
Phenolic acid	Caffeic acid, Chlorogenic acid, Coumaric acid and Derivatives, Gallic acid, Ursolic acid, Rosmarinic acid	Amzad *et al.* (2010), Boyer and Liu (2004), Ceymann *et al.* (2011), He and Liu (2007), He and Liu (2008), Hossain *et al.* (2009)
Phytochemicals of Lemon		
Flavonoids	Limettin, Quercetin and Vicenin-2	Akhila *et al.* (2009), Ghasemi *et al.* (2009), Gorgus *et al.* (2010), Ortuno *et al.* (2011), Ramful *et al.* (2011)
Vitamin	Ascorbic acid	Burdurlu *et al.* (2006), Ramful *et al.* (2011)
Phytoalexin	Scoparone	Ortuno *et al.* (2011)
Terpene	Limonene, β-Pinene, Neral, Geraniol	Gattuso *et al.* (2007), Pandey *et al.* (2010), Vekiari *et al.* (2002)
Phytochemicals of Papaya		
Vitamin	Ascorbic acid, Vitamin A, Vitamin B9& B12	Imaga *et al.* (2010b)
Flavonoid	Kaempferol, Quercetin, Myricetin and Rutin	Miean and Mohamed (2001), Rivera-Pastrana *et al.* (2010)
Phenolic acid	Ferulic acid, Chlorogenic acid, Caffeic acid, p-Hydroxybenzoic acid and Vanillic acid	Canini *et al.* (2007), Rivera-Pastrana *et al.* (2010) Zhou *et al.* (2011)
Esters	Benzaldehyde; β-damascenone and benzyl isothiocyanate	Lee *et al.* (2010)
Anthracene derivative	Anthraquinone	Ayoola *et al.* (2008), Imaga *et al.* (2010a)
Carotenoids	Lycopene and β-carotene	Rivera-Pastrana *et al.* (2010)

Hussein *et al.*, 2010; Karthishwaran and Mirunalini, 2010; Asmawi *et al.*, 2011). These are also responsible for the protective effects against inflammation, oxidation, neural-degenerations, etc. hence these chemicals inhibits the metabolic-dysfunctioning (Ekor *et al.*, 2006; Oloyede *et al.*, 2008; Nirmala *et al.*, 2008; Potchoo *et al.*, 2008; Wahab *et al.*, 2009; Sivabalan and Anuradha, 2010; Hasani-Ranjbar *et al.*, 2010; Patil and Patil, 2011; Lawal *et al.*, 2011). The papaya leaf extract, apple and lemon juice have been recommended by the folks to treat dengue fever but there is very little scientific literature available to support the use of these plant remedies. So in next section some of the important phytochemicals have been explored with reference to their potential therapeutic attributes (Table 1).

PHYTOCHEMICAL SIGNIFICANCE OF APPLE

Apple is from one of the major fruits of Northern areas of Pakistan and has many medicinal uses (Sher *et al.*, 2010). The methanolic and acetonic extracts of apple pomace have antioxidant and antiviral activity against some viruses (Suarez *et al.*, 2010). One of apples' phytochemicals 'phytoestrogens' has the potential anti-dengue property, it is also found in other fruits and have strong antiviral actions (Torres-Sanchez *et al.*, 2000; Martin *et al.*, 2007; Ogbuewu *et al.*, 2010).

Sialic acid is an essential requirement of eukaryotic cells and accounted for the normal development (Schwarzkopf *et al*., 2002; Balcan and Sahin, 2006; Senthil *et al*., 2007; Pavana *et al*., 2008; Mathur *et al*., 2010). Dengue causes the oxidative stress in the body by oxidating the plasma proteins and lowering the sialic acid concentration (Rajendiran *et al*, 2008). Thus antioxidants can help in maintaining the protein structure disturbed by oxidative stress. Apple contains many strong antioxidants like catechin and phloridzin (Boyer and Liu, 2004; Gilani *et al*., 2006; Beg *et al*., 2008; Gupta *et al*., 2008; Falah *et al*., 2008; Lelono *et al*., 2009; Rivas-Arreola *et al*., 2010; Kaur and Saraf, 2011), which can reduce the oxidative stress. The strong antioxidant like reduced glutathione (GSH) has the capability to inhibit the dengue production in the body and hence reduce the virulence of dengue (Tian *et al*., 2010). The apple juice has the excellent antioxidant ability; also promote the expression of anti-oxidating glutathione enzyme genes (Kujawska *et al*., 2011; Soyalan *et al*., 2011). The peels of unripe apple have oligomeric procyanidins, which simulate the innate immunity responses in DENV-infected cells (Kimmel *et al*., 2011). Many other procyanidins e.g. B1, B2, C1 etc. are also found in apple and procyanidin B2 was also detected in the human serum after the intake of procyanidin-rich food (Sano *et al*., 2003; Shoji *et al*., 2003). Procyanidins may have antiviral activities e.g., procyanidin B1 inhibits the hepatitis C virus by suppressing its RNA synthesis (Li *et al*., 2010; Zhuang *et al*., 2009). In Huh-7 cells procyanidin B1 showed concentration dependant effect against virus. Depending on this information this can be said that the procyanidins found in apple might have some antiviral activity. Thus apples not only directly can reduce the dengue infections but it also possesses indirect beneficial effect on dengue affected persons.

Catechin, the most active antioxidant flavonoid is found in apples and results based on HPLC and GC/MS studies showed its concentration 1.01 mg/kg w/w of apples (Sim *et al*., 2010). According to Pignatelli *et al*. (2006) catechin only in combination with quercetin can cause the recruitment of platelets. This recruitment of platelets was resulted by the inhibition of PKC-dependent NADPH oxidase activation. Coumaric acid is another medicinally known compound found in apple. p-Coumaric acid (isomeric form of coumaric acid) has antioxidant, anti-coagualtory and hepato-protective activity with high absorption in the rats' gut (Choi *et al*., 1998; Lee *et al*., 2008; Luceri *et al*., 2007; Zhang *et al*., 2007). It can reduce the ethanol caused oxidation and can inhibit the ADP-induced platelets aggregation by enhancing the plasma antioxidant activity. In addition it also reduces the thromboxane B2 production, which occurs during ADP-induced aggregation but it doesn't showed any effect on platelet count and mean platelet volume. Coumaric acid contents of apple may be beneficial in reducing the oxidation and inflammation problems caused by dengue infections.

A gas chromatography-mass spectrometry study on apple skin confirms the presence of an anti-oxidant compound called rosmarinic acid (Amzad *et al*., 2010; Koroch *et al*., 2010). Rosmarinic acid has a potential antiviral activity against Japanese Encephalitis Virus and HIV-1 (Dubois *et al*., 2008; Swarup *et al*., 2007). It inhibits the replication of both of these viruses. It also possesses the antithrombotic effect in the wistar rats' vena cava, which may be due to the inhibition of collagen induced platelets aggregation (Zou *et al*., 1993). Thus this can be said that apple is a rich source of phenolic and polyphenolic compounds which are of significant medicinal importance. Some of these compounds have antiviral effects, which may play role in controlling the dengue virus but further investigation is still required.

PHYTOCHEMICAL SIGNIFICANCE OF LEMON

Lemon is a common cultivated plant in Pakistan, where in some areas its fruits are used commonly to treat the teeth problems (Hussain and Ishtiaq, 2009; Hussain *et al*., 2010). But many other characteristics can also be ascribed to this plant due to the presence of a range of important phytochemicals (Table 1). Scoparone is a phytoalexin; an immunoregulatory compound of lemon, which induce the reduction in NO levels by suppressing the expression of iNOS genes (Kim *et al*., 2007; Ortuno *et al*., 2011; Yang *et al*., 2008b; Yang *et al*., 2009). Thus immunoregulatory activity of scoparone could be considered as positive role in treating the dengue caused immunological problems. The other biologically important antioxidant compound of lemon is Vicenin-2, a flavonoid, which may has the anti-inflammatory activity (Aquila *et al*., 2009; Barreca *et al*., 2010; Ramful *et al*., 2010). Another medicinally important compound, limonene is the natural terpene found in different plants including lemon, has low toxicity; it reduces the heart burn and gastroesophageal reflux in dosage dependant manner (Al-Howiring, 2003; Talei and Meshkatalsadat, 2007; Gattuso *et al*., 2007; Meshkatalsadat and Mirzaei, 2007; Yoon *et al*., 2009; Di Vaio *et al*., 2010; Sun, 2007). It cause an increase in the concentrations of cytosolic calcium and cAMP and proteins kinase activity, which may energize the antiviral and anti-inflammatory immune responses (Hirota *et al*., 2010; Park *et al*., 2010; Romeilah *et al*., 2010). The curative properties of lemon can also be enjoyed by utilizing its essential oils, which have the excellent antioxidant property (Campelo *et al*., 2011). The other compounds of lemon with antioxidant property are neral, neryl acetate and geraniol (Tansi and Nacar, 2000; Vekiari *et al*., 2002; Meftahizade *et al*., 2010; Kadri *et al*., 2011). Thus lemon has many phytochemicals which can support the immune responses against virus caused problems, especially through its anti-oxidant agents.

PHYTOCHEMICAL SIGNIFICANCE OF PAPAYA

Carica papaya is an important plant with significant medicinal properties e.g. anti-inflammatory, antimicrobial and wound management (Rahmat *et al*., 2002; Saeed and Tariq, 2006; Raji *et al*., 2006; Zakaria *et al*., 2006; Oladunmoye and Osho, 2007; Idu and Onyibe, 2007; Oladimeji *et al*., 2007; Goyal *et al*., 2009; Ajlia *et al*., 2010; Ansari *et al*., 2011; Osadolor *et al*., 2011). It is also an important source of many phytochemicals (Table 1). On administration of papaya in its powder form at the rate of 5 mg kg^{-1} of body weight, it can significantly increase the platelet count of dengue infected patients (Sathasivam *et al*., 2009). In another research it is found that its leaf aqueous extracts are responsible for a significant increase in platelets count, white blood cells and neutorphils in dengue infected patient (Ahmad *et al*., 2011). The fermented preparations of this fruit have antioxidant activity; it increases the reduced glutathione concentration in red blood cells and decreases the reactive oxygen species (Fibach *et al*., 2010). The papaya extracts also shows the positive effects on other immune responsive cells like macrophages; its extracts have a positive effect on the macrophage antiviral properties (Lidbury and Mahalingam, 2000; Rimbach *et al*., 2000; Ishikawa and Miyazaki, 2005; Mahbub-E-Sobhani *et al*., 2011; Du *et al*., 2011). The macrophages upon viral infection are responsible to produce antiviral antibodies. So this can be said that papaya may have many healthy effects on dengue infected patients due to its positive regulation of macrophages and platelets.

The medicinal importance of papaya phytochemicals is elucidated here to make an awareness of its remedial uses against dengue caused problems. Anthraquinone an important photochemical of may plants also found in papaya either in free or in bound form and many studies reported that

various anthraquinones have antiviral property against different viruses (Semple *et al*., 2001; Li *et al*., 2007; Kumar *et al*., 2007; Hassan *et al*., 2007; Imaga *et al*., 2010a; Sonibare *et al*., 2011; Xiong *et al*., 2011). The anthraquinone derivatives also possesses the anti-coagulatory activity, its derivatives have the potency to reduce the thrombin, arachidonic acid, collagen and platelet-activating factor-induced platelet aggregation (Baqi *et al*., 2009; Gan *et al*., 2008). These derivatives have potential to activate the $CD34^+$ dendritic cells, which is important for immunological responses (Van de Ven *et al*., 2011). The anthraquinone derivatives are also important in stimulating the proliferation of resting human peripheral blood mononuclear cells and lymphocyte (Cherng *et al*., 2008). Another therapeutic compound of papaya is myricetin, which possess the in vitro anti-inflammatory activity and can reduce the acetic acid-induced capillary permeability (Miean and Mohamed, 2001; Wang *et al*., 2010). It also has the sedative activity against chemical (acetic acid and formalin) caused neural problems; it may also have the anti-platelet activity (Tong *et al*., 2009). So both of these compounds have anti-inflammatory effects and can modulate the immunological anti-dengue responses.

Another flavonoid 'kaempferol' present in papaya, which showed antimicrobial (Taechowisan *et al*., 2008) and strong anti-inflammatory activity by reducing the NO levels (Hamalainen *et al*., 2007). It is responsible for dose dependent reduction in NO levels, which was governed by the reducing in iNOS proteins and mRNA expression. Papaya is an important source of some vitamins like vitamin A, B12 and Folic acid, which might have some contribution in its therapeutic properties (Iyawe and Onigbinde, 2006; Wall, 2006; AL-Sowyan, 2009; Imaga *et al*., 2010b; Jiao *et al*., 2010). Vitamin B 12 deficiency can cause abnormalities in central nervous system, which may increase the complications in dengue patients with already affected nervous system (Bordignon *et al*., 2008; Scalabrino, 2009; Yauch and Shresta, 2008). Thus the presence of vitamin B 12 may has healthy impact on dengue infected patients. Deficiency of vitamin A may also contribute to immune defects and can increase the prevalence of several diseases (Saeed *et al*., 2005; Lin *et al*., 2008b; Sommer, 2008; Uboh *et al*., 2008; Uboh *et al*., 2009; Qiu *et al*., 2010; Iribhogbe *et al*., 2011). Dengue virus causes aplastic anemia which can be inhibited by the application of folic acid (Albuquerque *et al*., 2009; Ganji and Kafai, 2009). Iron-folic acid can decrease the rate of anemia especially in women; by the increasing the haemoglobin levels (Casey *et al*., 2010). It also protects the endothelial cells from the oxidative stress by increasing the expression of dihydrofolate reductase (Gao *et al*., 2009). Dihydrofolate reductase regulates the tetrahydrobiopterin and NO superoxide production to suppress the oxidative stress (Crabtree *et al*., 2011). Ferulic acid a form of phenolic acid is an important subject of antioxidant activity and so can protect the body from many health problems including neural disorders (Kanski *et al*., 2002; Srinivasan *et al*., 2007). Its antioxidant property is basically due to its functional hydroxyl and phenoxy groups. Lycopene is another anti-oxidant compound of papaya. It has the potential antioxidant property and thus inhibits the liver from oxidative stress (Seren *et al*., 2008) and might be helpful to reduce the HCV related complications. Bignotto *et al*. (2009) studied the anti-inflammatory effects of lycopene in two rat models. It was observed that lycopene impose a strong anti-inflammatory activity at 25 and 50 mg kg^{-1} concentrations in both paw oedema and ischaemia-reperfusion models of rat. Herzog *et al*. (2005) noted that lycopene administration causes a decrease in inflammation causing agents like interleukin-1β, CXC chemokines, etc. Thus lycopene is an efficient anti-inflammatory agent and it also showed preventive effect on chromosomal aberrations (Aslanturk and Celik, 2005). Another phenolic acid named 'vanillic acid' is also present in papaya and some other plants (Mehboob *et al*., 2000; Tajuddin *et al*., 2002; Shaukat *et al*., 2003;

Jazayeri *et al*., 2007; Zhou *et al*., 2011). Vanillic acid possesses a strong hepatoprotective activity, as it decreases the activity of transaminase enzyme and disorganized hepatic sinusoids (Itoh *et al*., 2009). In addition, it also protects the liver from immune-induced liver injuries by decreasing the concentration of inflammatory cytokines, interferon (IFN)-gamma and other liver infecting agents. This investigation of papaya properties shows that papaya has many therapeutic properties and it is a rich source of highly protective biological compounds, which can treat many health problems.

SHARED PHYTOCHEMICALS AND THEIR SIGNIFICANCE

The three studied fruits have some common curative phytochemicals like ascorbic acid (vitamin C) and quercetin (Akhila *et al*., 2009; Bari *et al*., 2006; Ghasemi *et al*., 2009; Li *et al*., 2008b; Sultana and Anwar, 2008; Ramful *et al*., 2011; Wach *et al*., 2007). The curative antioxidant ascorbic acid is an important coagulatory nutrient, which may reduce the severity of oxidation and anticoagulation problems of dengue infection (Fromberg *et al*., 2011; Savini *et al*., 2007; Padayatty *et al*., 2003). It has other remedial properties, which may able to treat dengue caused problems. Like, it has hypotensive property and can reduce the vascular tension in Stroke-Prone Spontaneously Hypertensive Rats (SHRSP) (Chen *et al*., 2001; Sato *et al*., 2011a). It can strongly reduce the oxidative stress in mice liver caused by high iron diets but it did not play any role in maintaining the physiological processes under low iron concentrations (Premkumar *et al*., 2007). Ascorbic acid also have anti-inflammatory responses, it significantly reduce the amount of inflammation causing C-reactive protein (Black *et al*., 2004; Block *et al*., 2009; Du Clos and Mold, 2004). Thus ascorbic acid in the presence of physiologically enough iron may be an important candidate of antioxidant properties. Quercetin is a strong antioxidant candidate (Cibin *et al*., 2006; Jun *et al*., 2007) and can modulate the memory impairments (Sternberg *et al*., 2008; Naseri *et al*., 2008; Ebrahimzadeh *et al*., 2009; Bahri-Sahloul *et al*., 2009; Tota *et al*., 2010). It also acts as an anti-inflammatory agent and protects the body from kinase activity of platelet, which cause coagulation (Bischoff, 2008; Navarro-Nunez *et al*., 2010; Van der Meijden and Heemskerk, 2010). It doesn't has direct effect on coagulation causing stimulus (like thrombin) instead it interfere with the signaling pathway and stops the platelets aggregation (Nunez *et al*., 2009).

Caffeic acid and chlorogenic acid are the two phenolic acids shared by the papaya and apple (Bouayed *et al*., 2007; Boyer and Liu, 2004; Chinnici *et al*., 2004; Canini *et al*., 2007; He and Liu, 2008; Rivera-Pastrana *et al*., 2010). Caffeic acid has the antiviral property, its application before the infection can effectively reduce the replication of herpes simplex virus type 1 (Ikeda *et al*., 2011). The caffeic acid esters have noteworthy antioxidant properties, it possess negative effect on the collagen-induced platelet aggregation (Bakasso *et al*., 2008; Hsiao *et al*., 2007; Jayaprakasam *et al*., 2006). Its ester causes the direct inhibition of collagen binding to the platelet by binding to the platelets' collagen receptor. Hence it reduces the collagen induced platelet aggregation, which may help to cope with heart problems of coagulation. Caffeic acid is also produced in intestine by the hydrolyzation of chlorogenic acid; chlorogenic acid is an antioxidant polyphenol (Sato *et al*., 2011b). But caffeic acid has more pronounced antioxidant effects than chlorogenic acid. The chlorogenic acid plays role in anti-inflammatory reactions by inhibiting the neutrophil locomotion and adhesion (Hebeda *et al*., 2011).

All studied fruits are good source of important phytochemicals, which possesses different biological properties. The phenolic compounds of these studied fruits have chief antioxidant property, which is important for treating many health problems. The variety of phytochemicals

provides variety of benefits to health as the phytochemicals have positive effects on immune-responsive cells. They also provide benefits to memory impairments.

CONCLUSION

Dengue is a vector born disease with a complex mechanism of action, as it can directly or indirectly destroy the activity of many immune cells. Its adverse effects are due to highly suppressed immune responses through IgM antigen of dengue. Figure 1 shows a general layout scheme for the approaches to deal with dengue virus. Its vector control appears to be the best approach because antiviral drugs are not much successful for this disease. Vaccines for dengue could be another preventive measure but these vaccines are still in developmental phase. In addition, these antiviral drugs and vaccines are not much common in developing countries where this disease is transforming into an epidemic. After viral infection treatment totally concentrates either in the suppression of viral particles or reduction in the severity of related complications. Papaya and apple both comprised of phytochemicals that have potential antiviral activities but lemon was only found useful in dealing with secondary complication issues. All of these three plants have significant antioxidant activities which might be helpful in reducing the indirect oxidant effects of this virus on different human tissues. After dengue infection the best approach seems to be the improvement of patient's immune response, especially the platelets count in body. Papaya and apple both have been reported for their ameliorating effects on immune system. On the basis of reviewed literature it can be concluded that both papaya and apple have their potential use in the treatment of dengue. There is future need of clinical studies to deeply investigate the phytochemistry of papaya and apple to identify their best possible use in the treatment of dengue fever. In a developing country like Pakistan with weak health care system the use of medicinal plant (such as apple and papaya) should be promoted as cheaper and easily available alternate medicine source to deal with epidemic diseases like dengue.

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