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Naturally Occurring Alternative Treatment Model of Chloroquine/Hydroxychloroquine + Azithromycin + Antiallergic Medications effective in COVID-19 suspected Symptomatic patients: An Indian perspective

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Abstract: Whole world is fighting against single enemy, novel corona virus (nCoV) causing respiratory trouble, the disease originated from Wuhan of China at the end of 2019 (COVID-19) which is very much similar with the corona virus causing severe acute respiratory syndrome, the disease outbrocken in 2003 (SARS). That is why nCoV is also called SARS-CoV-2/2019-nCoV. Present world is exhausted under massive lockdown and becoming looser day by day. No specific treatment yet to be established except repositioning of some old drugs, though they possess risky side effects. At this juncture to overcome adverse side effects of such drugs, aiming to search naturally occurring candidates targetting to establish a treatment model and to combat the challenge. The traditional plants/spices of bitter taste from Indian origin like *Azadirachta indica* A. Juss. (Indian Lilac/Neem/Nimtree), *Andrographis paniculata* (Burm. f.) Nees (green chirata/Indian kalmegh), *Momordica charantia* L. (bitter gourd/bitter melon/Indian karela), *Moringa oleifera* Lam. (Tree of life/Miracle-/Drumstick-/Horseradish tree), *Curcuma longa* L. (turmeric/Indian Haridra) rhizome and *Nigella* sativa L. (Black Cumin/Kalonji/Indian Kalojeera) seeds commonly pose the antimalarial, antidiabetic, antihyperlipidemic, anti-inflammatory/antiarthritic, immunomodulatory, and antiviral bioactive behaviors as therapeutics. Chloroquine/Hydroxychloroquine are resembled the same behaviors concomitantly. Both chloroquine(CQ) and hydroxychloroquine(HCQ) are synthetic antimalarial and antiarthritic drugs but recently repurposing the antiviral activity against SARS-CoV-2. CQ exhibits adverse side effects like vision loss, psychiatric disorder, cramp etc.. But HCQ, hydroxylated derivative of CQ is less toxic than CQ. HCQ on the other hand, it has been linked to some instances of cardiac arrhythmia, macular disorder and liver damage. Present study aiming to evaluate naturally occurring preventive/prophylactic/alternative potentials from Indian perspective searching database from existing literature and internets to overcome such odd side effects of CQ/HCQ on human subjects. The common/signature bioactive behaviors of some Indian traditional bitter plants/spices (SITBP/S) mentioned above and CQ/HCQ are more or less are found to be similar. Moreover SITBP/S exhibits anthelmintic and antiulcer good effects found from literature. Also a di-/tri-/polyherbal formulation could be suggested by constructing a Common-base-tetra-triangular (CBTT) model for traditional treatment thus proposed and implimented on a very small group of COVID-19 suspected symptomatic patients from my Institute at preliminary level, especially as preventive/prophylactic or alternative antiviral approach to SARS-CoV-2, might be rationalized to replace the CQ/HCQ side effective treatment. CBTT model of treatment + azithromycin (AZ) were implimented in presence or absence of antiallergic medications (AAMs) in suspected symptomatic patients those who were denied to go Hospital. Without the AAMs, 7 days delay of recovery was observed. Resulting CBTT model +AZ + AAMs could be repurposed for faster recovery.

Keywords*:* COVID-19, CQ/HCQ: reposition and side effects, reposition of other drugs, SITBP/S and CBTT treatment model

Abbreviations

AALHAE – *Abroma augusta* leaf-hydroalcoholic extract

AAMs - Antiallergic medications (Montelukast + Levocetirizine)

ADM - Anti-diabetic medication

ADMET – Absorption, distribution, metabolism, excretion, toxicity

AGEs – Advanced glycation endproducts

AHTNM- Anti-hypertensive medication

AI – *Azadirachta indica*

AP – *Andographis paniculata*

AZ – Azithromycin

A1C(HbA1C) – Glycated hemoglobin

BDAC – Twice daily before meals

CBTT – Common base-tetra-triangular

CIA – Collagen induced arthritis

CL – *Curcuma longa*

CVB-3/4 – Coxackievirus B-3/4

DHF- Diherbal formulation

DM – Diabetes mellitus

DENV – Dengue virus

EBV – Epstein-barr virus

FMDV - Foot-and-mouth disease virus

HAART – Highly active anti-retrovial therapy

HBV – Hepatitis B virus

HDL – High density lipoprotein

HF – Herbal formulation

HHF – Hexa herbal formulation

HIV – Human immunodeficiency virus

HSV – Herpes simplex virus

HTLV-1 – Human T-cell leukemia virus type 1

HTN – Hypertention

IDDM – Insulin dependent diabetes mellitus

ISHAE – Institute supplied hydroalcoholic extract

JEV – Japanese encephalitis virus

LCZ – Levocetirizine

LDL – Low density lipoprotein

MC- *Momordica charantia*

MLK – Montelukast

MO – *Moringa oleifera*

NDV – Newcastle disease virus

NIDDM - Non-insulin dependent diabetes mellitus

NO – Nitric oxide

NS – *Nigella sativa*

PenHF – Penta herbal formulation

PHF- Polyherbal formulation

PPAR-g – Peroxisome proliferator activated receptor gamma

PPI – Proton pump inhibitor

RA – Rheumotoid arthritis

SARS-CoV – Severe acute respiratory syndrome causing corona virus

SINV – Sindbis virus

SITBP/S – Some Indian traditional bitter plants/spices

SOS – If occasion require, if necessary

SPAE – Self prepared aqeous extract

SRV – Simian retro virus

STZ- Streptozotocin

TC – Total cholesterol

TDAC – Thrice daily before meals

TetHF – Tetra herbal formulationn

TG – Triglycerides

THF – Tri herbal formulation

TQ – Thymoquinone

VLDL – Very low density lipoprotein

INTRODUCTION

COVID-19: Commonly referred to as the “novel coronavirus" (nCoV) or simply the “coronavirus", a new virus showing a respiratory illness like pneumonia, or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a causative agent for corona disease 2019 (COVID-19). WHO declared a highest global health emergency on COVID-19, a contagious disease on 30th January 2020, that time outside of the China only 98 case of positive were found (1). But today, the 7th July 2020 the figure is totally opposite that the world is overwhelmed by more than 1 crore 15 lacs infections and 5.3 lacs death. The rate curve of world confirmed cases of COVID-19 and confirmed death from COVID-

19 showed still steeper. No flattening the curves were observed (source: Johns Hopkins CSSE Note, data updated on yesterday, 6th July 2020) (2). Medical professonals are facing direct challenge due to unprecedented power of spreadibility of the virus. At this moment Mankind and world economy are totally jeopardized by lockdown. Still, there is no other options except maintaining social distance, masking, hand hygiene, testing, tracing and isolation. Only the way to wait for a specific medication and or a vaccine to defeat the virus. Currently there are no FDA approved vaccines available for COVID-19. Clinical trials and case reports have yield moderate results repurposing antiviral therapies used in unrelated viral infections, but further investigation is required (3). SARS-CoV-2 whether it a Lab-made or Nature-made, the theory of conspiracy was debunked (4,5).

CQ/HCQ: Background- the pharmacology of chloroquine and hydroxychloroquine, which is similar for both drugs (6) but the details are different. For example, both drugs are partially excreted in feces, but the proportions differ slightly—8–10 % for chloroquine and 15–24 % for hydroxychloroquine. Generally, whatever is said in this chapter about one drug can be assumed to apply to the other unless otherwise specified. Because both drugs are derivatives of a 4-aminoquinoline (4AQ) nucleus (7). CQ has bitter taste, was described by Hans D Nothdurft and Kevin C Kain. (8). and HCQ- it leaves a horrible bitter taste in the mouth, reported in India Today Insight (9). **Therapeutic property-** Therapeutics as antimalarial, antidiabetic, anti- inflamatory/antiarthiritic, immunomodulatory, antiviral activities etc. and pharmacological importance were reviewed by Katelyn A. Pastick *et al.*, 2020 (10). **Antimalarial-** Chloroquine phosphate and hydroxychloroquine sulfate are substituted 4-amino quinoline compounds that differ only by a hydroxy group. They are basically two antimalarial agents (11). **Antidiabetic**- *In vitro* and *in vivo* animal studies have shown that HCQ and the parent drug CQ affect insulin metabolism. CQ increases insulin binding to its receptor and alters hepatic insulin metabolism, potentiating insulin action (12,13). Streptozocin-induced diabetic rats treated with HCQ had lower insulin clearance and subsequently lower glucose levels (14,15). Long-term use of CQ enhanced insulin secretion in rats (16). Glycated hemoglobin A1C(HbA1C) was successfully reduced to target by HCQ treatment (17). **Antihyperlipidemic-**3 days of oral chloroquine treatment improved abnormalities of lipoprotein metabolism in patients with NIDDM (18). Improvement of low density lipoprotein cholesterol (LDL-C) level was observed on HCQ theraphy of human subject with IDDM (19). **Antiarthritic and immunomodulatory-** The antimalarial agents chloroquine and hydroxychloroquine have been used widely for the treatment of rheumatoid arthritis and systemic lupus erythematosus. These compounds lead to improvement of clinical and laboratory parameters, but their slow onset of action distinguishes them from glucocorticoids and nonsteroidal antiinflammatory agents. Chloroquine and hydroxychloroquine increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and posttranslation modification of proteins in the Golgi apparatus. It is proposed that the antirheumatic properties of these compounds results from their interference with "antigen processing" in macrophages and other antigen-presenting cells. Acidic cytoplasmic compartments are required for the antigenic protein to be digested and for the peptides to assemble with the alpha and beta chains of MHC class II proteins. As a result, antimalarials diminish the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells and result in down-regulation of the immune response against autoantigenic peptides. Because this mechanism differs from other antirheumatic drugs, antimalarials are well suited to complement these other compounds in combination drug therapy (20). **Anti-HIV-1 activity-** CQ and its derivative HCQ are endĺowed with a broad anti-HIV-1 activity inhibiting X4, R5 and X4/R5 stains (21). **Anti-COVID-19 activity-** Both CQ and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles such as endosomes/lysosomes, essential for membrane fusion (22). In addition CQ could inhibit SARS-COV-2 entry through changing the glycosylation of ACE 2 receptor and spike protein(23). HCQ effectively inhibited the entry step as well as the post-entry stages of SARS-CoV-2. HCQ is a less toxic derivative of CQ is effective in inhibiting SARS-CoV-2 infection *in vitro*(24). Both CQ and HCQ can inhibit SARS-CoV (2003) and SARS-CoV-2 before and after infection (10).

Repositioning of antimalarial drugs CQ/HCQ as antiviral agents of COVID-19: Chloroquine is a cheap, widely available drug that has been routinely used since 1945 against malaria and other conditions and can be safely taken by pregnant women and children. Lab studies found the antiviral drug was effective against the coronavirus, at least in a petri dish, and results from a small French study in 24 patients, announced this week, suggested that it could quicken recovery. Doctors said 25% of patients who received the drug tested positive for the virus after six days, compared with 90% of those who did not receive it. Chloroquine and a related drug, hydroxychloroquine, are among the four treatments tested in an international clinical trial, announced on Wednesday by the World Health Organization (WHO), and the UK has added chloroquine to its list of medicines under export controls (25).

Side effects of CQ/HCQ on human subjects: Precise knowledge of the undesirable effects of chloroquine and hydroxychloroquine allows better exploitation of their therapeutic effects. Retinopathy can be avoided by observing a maximum daily dosage of 3.5-4 mg/kg ideal body weight for chloroquine and 6-6.5 mg/kg for hydroxychloroquine. In this way, both can be used for long-term therapy. The pharmacokinetics of chloroquine (storage in deep compartments with long plasma half-life) means that it can cumulate, especially with higher dosages and in the presence of renal or hepatic insufficiency. A high plasma concentration reinforces the side-effects without reinforcing the therapeutic effects. Besides subjective symptoms (e.g. anorexia, diarrhoea, nausea), the following undesirable reactions are significant. On the skin exanthema, hyperpigmentation and photodynamic reactions can develop. The hair can become white in blonde and red-haired men. In the eye, chloroquine deposits in the cornea and disturbances of accommodation can occur, besides retinopathy. Neuromyopathy and central nervous system disturbances (e.g. psychosis) are rare, as is impairment of auditory function or blood cells. During pregnancy there is a risk of potential fetal damage (hearing loss, abortion). An acute overdose is extremely dangerous: the lethal dose is 1 g for children and 4g for adults. As death occurs rapidly, chloroquine has to be stored where it is absolutely inaccessible to children (26). Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart (27). ROSIE MCCALL reported that some swedish hospitals have stopped using CQ to treat COVID-19 after report of severe side effects. Hospitals in Vastva Gotaland region in Sweden are no longer offering the antimalarial medications with side effects reported to include cramps and the loss of peripheral vision. One of the patients offered was Carl Sydenhag a 40 year old Stockholm resident. Sydenhag was prescribed two tablets of CQ to take daily after he was diagnosed with COVID-19 on March 23. But instead of making him feel better, the medication produced unpleasant side effects. As well as cramps and vission loss, Sydenhag experienced a headache that felt like stepping into ‘a high voltage plant' he told the paper (28). CQ and HCQ include QTc prolongation and the resultant risk of ventricular arrhythmias and other side effects were reviewed by Katelyn A. Pastick *et al.,* 2020 (10).

ICMR launched study on **side effects of hydroxychloroquine**. The study-report described that some health care workers in India who self-medicated themselves with anti-malarial drug hydroxychloroquine showed side effects like abdominal pain, nausea and hypoglycemia. “The average age of such health workers were 35 years. The most visible side effect was that of abdominal pain which was reported in ten per cent of all those who consumed the medication while nausea-like symptoms were reported in 6 per cent. A fewer proportion — around 1.3 per cent — had hypoglycaemia. The study so far revealed that 22 per cent of these health care workers who consumed HCQ had existing co-morbidities like diabetes or blood pressure problems or vascular-related ailments or respiratory illnesses and they started taking the drug out of fear of contracting the disease. 14 per cent of them did not even got their ECG checked before having it (29).

It is pertinent to say that once I took an attempt aiming to overcome psychiatric disorder developed due to CQ treatment, simultaneously an antipsychotic drug chlorpromazine was chosen for *in vitro* binding study on ion transporting ATPase, the enzymes were purified from rat brain and goat testes, considering as the 2nd part of my Ph.D.thesis, from Department of Chemistry, Bose Institute, Kolkata, resulting a research article “The effect of binding of Chlorpromazine and CHLOROQUINE to ion transporting ATPases" was published in Molecular and Cellular Biochemistry vol. 198, pp. 179-185, 1999. Also another research article entitled “Interaction of chlorpromazine with low molecular mass ion-transporting ATPase modulator proteins from rat brain cytosol", was published in Indian Journal of Biochemistry & Biophysics vol. 36, pp. 82-87, 1999. In both of the papers I was 1st and co-authored with Prof. Parimal C. Sen of the said department.

Ulcer effect of CQ/HCQ : The use of Chloroquine may be dangerous to the integrity of the stomach, especially in existing gastric ulcers. It increases oxidative stress in the gastric mucosa caused by indomethacin and acidified ethanol (30). HCQ- Antirheumatic drugs may include unspecifical gastrointestinal symptoms like nausea, vomiting and diarrhea as well as induction of ulcerative mucosal lesions (methotrexate) and occurrence of a hepatopathy, can lead in some cases of a monotherapy (hydroxy-/chloroqine, sulfasalazine) or combination therapy (methotrexate + leflunomide) to a fulminant hepatitis (31).

Reposition of other drugs:

Repositioning of anti-HIV drug Kaletra: Kaletra is combination of two antiviral medicines, lopinavir and ritonavir normally used to treat HIV which lab studies suggested held promise as a potential COVID-19 treatment. However these hopes suffered a significant setback with one of the major studies of 200 seriously ill patients from China finding no benefit. It is possible that the drug could be effective if given earlier on or to less severely ill patients. The WHO has included kaletra in a major multi country trial. (25).

Repositioning of anti-ebola drug Remdesivir: Remdesivir was originally developed as an Ebola treatment, but the drug has emerged as a front-runner among potential antiviral drugs to combat covid-19. The enthusiasm comes from studies that show that works against SARS and MERS, two other coronaviruses that are more lethal but less transmissible. The drug works by shutting off the virus's ability to replicate itself inside cells. This means it is most likely to be effective when a person has just caught the bug and the virus is still reproducing in the upper respiratory track. One reason for caution is that early data suggest people may already have high levels of the virus when they start showing symptoms. Multiple trials are under way to evaluate remdesivir in China, the US and Asia (25). But hoping a good news, that preliminary results from a trial conducted by the U.S. National Institutes of Health showed that remdesivir cut hospital stays by 31% compared to a placebo (32).

Repositioning of Japanese anti-flu drug Favipiravir: The japanese flu drug made by a subsidiary of Fujifilm, has created a stir by more than halving the time that people with covid-19 test positive for the virus. A chinese trial in 340 people showed that the virus tended to be cleared in four days in those who received the drugs, versus 11 days in those who went without. Chest scans supported the findings revealing less damage in those who took the drug. But the antiviral also known as avigan may need to be given before virus levels peak in the body. A japanese health official told the Mainichi Shimbun newspaper that it did not appear to work as well in severely ill people, in whom the virus had more time to replicate (25), though it recently showing a hope.

Repositioning of an antiparasitic drug Ivermectin: The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in* vitro (33). Past research has suggested that it may also be able to fight off some viruses including HIV-1 and dengue virus. A new study in cell cultures suggests that ivermectin (33) existing antiparssitic drug is able to eliminate SARS-CoV-2 within 48 hours. However whether this approach is safe and effective in human being remains to be seen(34). Though, a medical team from Bangladesh, said a frequently used antiprotozoal medicine called Ivermectin in a single dose with Doxycycline, an antibiotic, yielded virtually the near-miraculous results in curing the patients with COVID-19 (35).

Repositioning of an antacid drug Famotidine: Famotidine is an antihistamine that reduces the acid produced in the stomach, hence easing heart-burn. It is used in the treatment of acid reflux and peptic ulcers. The drug has been perceived as "generally safe", with common side-effects including headache and diarrhoea. It is one of the oldest molecules, which has now been taken over by latest antiacids such as proton-pump inhibitors (PPIs). A cheap antacid is the latest drug stoking optimism among scientists and researchers seeking a cure for covid-19, the biggest pandemic the world has seen in decades. Famotidine sold under different brand names, including Famocid in India and Pepcid in the US, famotidine is currently the subject of a trial in the United States. The trial followed reports from China that multiple elderly Covid-19 survivors in Wuhan were found to be heartburn patients who had been taking the drug. Doctors who worked with above 80 had died, many among the survivor of coronavirus patients in Wuhan reportedly discovered that although one in five Covid-19 patients aged survivors had been "taking heartburn meds". Hospitalised COVID-19 patients on famotidine appeared to be dying at a rate of about 14% compared with 27% for those not on the drug, although the analysis was crude and the result was not statistically significant," *ScienceMagazine* noted in 26 April report (36).

Some Indian traditional bitter plants/spices (SITBP/S):

***Azadirachta Indica*: Background**- The Neem tree (*Azadirachta indica* A. Juss.) growing in tropical and subtropical regions, is a native tree of India. Neem belongs to Meliaceae family, also known as a Limbo, Nim, Nimba, Medusa and Vempu. It is also called "village pharmacy" of South Asia because of its enormous medicinal properties. Every part of Neem is so useful for the treatment of human disease. Various parts of the tree are well known for their medicinal properties which are prescribed by Ayurvedic, Siddha, and herbal medicine practitioners in India. Currently Azadirachta indica- Neem formulations are effective against a several diseases, ulcers, eczema, sores, burns, ulcers etc. It has been used in ayurvedic medicines for thousands of years (37). **Therapeutic properties**- It exhibits therapeutic

properties such as anti-viral, anti-fungal, anti-insecticidal, anti-bacterial, anti-allergic, anti-helminthic, anti-inflammatory, antidiabetic, immunostimulatory and anti-dermatic properties. Beneficial effects of Neem tree was reviewed by Sharique Ahmad *et al.*, 2019 (37). **Bio-active compounds-** Approximately 135 different structural compounds have been sequestered and identified from different part of Neem tree. a. Isoprenoids containing limonoids, protomeliacins, gedunin, azadirone, vilasinin and C- secomeliacins like salanin, nimbin and azadirachtin. b. Non-isoprenoids containing amino acids, polysaccharides, polyphenolics like flavonoids, sulphurous compounds, dihydrochalcone, glycosides, tannins, Coumadin and aliphatic compounds (37). **Antimalarial-** B. C. Akin-Osanaiya, A. J. Nok, S. Ibrahim et al conducted an experiment in which the antimalarial activity of extracts using Plasmodium berghei infected albino mice was used and reports led that Neem leaf and stem bark extracts reduced the level of parasitaemia in infected mice by about 51–80% and 56–87%, respectively (38). **Antidiabetic**- Reduces blood sugar level and precludes adrenaline and glucose-induced hyperglycaemia (39). **Antihyperlipidemic**- Azadirachta indica leaf extract significantly reduced the total cholesterol, LDL-and VLDL- cholesterol, triglycerides and total lipids of serum in streptozotocin induced diabetic rats, but HDL-cholesterol levels remained unchanged when compared with STZ induced diabetic control animals (40). **Analgesic, anti-inflammatory and antipyretic**- Neem leaf extracts have analgesic, anti-inflammatory and antipyretic effects in Albino rats (41). **Immunostimulant**- Activates cell-mediated immune pathways to provoke an enhanced response to subsequent mitogenic or antigenic encounter (42). Effect of Neem on NF-κB was demonstrated as NF-κB transcription factor plays a major role in cancer and related diseases (43). **Antiviral**- Treatment of fowl pox, smallpox, chicken pox, Vaccinia virus, warts, moderate inhibition of hepatits B virus, Chikungunya, herpes virus, and measles virus (44,45,46). The antiviral potential of a tetranortriterpenoid isolated from neem called gedunin against dengue virus (DENV) replication by targetting the host cheperone, Hsp 90 was evaluated (47). Results revealed that Neem bark extract (NBE) significantly blocked HSV-1 entry into cells at concentrations ranging from 50 to 100 μg/mL(46). Leaf extracts of Neem (Azadirachta indica, A. Juss.) (NCL-11) has shown virucidal activity against coxsackievirus B-4. Interference seen at an early event of its replication cycle (48).

***Andrographis paniculata*: Background-** *Andrographis paniculata* (Burm. f.) Nees originates from India and grows widely in many areas in Southeast Asian countries. It belongs to the family Acanthaceae. Importance and uses of medicinal plants are also stated in different religious books (i.e., the Holy Qur'an, the Bible). About 19 medicinal plants and 176 medicinal plants are mentioned in the Holy Qur'an and the Holy Bible, respectively. AP is one of the highly used potential medicinal plants in the world. *Andrographis paniculata* (Burm. f.) Wall. ex Nees (AP) is an important medicinal plant and widely used around the world. AP is used as a traditional herbal medicine in India, Bangladesh, China, Hong Kong, Pakistan, Philippines, Malaysia, Indonesia, and Thailand and is ethnobotanically used for the treatment of snake bite, bug bite, diabetes, dysentery, fever, and malaria. In the Unani and Ayurvedic medicines, AP is one of the mostly used medicinal plants In recent times, commercial preparations of this plant extracts are also used in certain countries. However, the preparations yet need to be standardized for their better efficacy (49). **Bioactive compounds-** Aerial part of AP is most commonly used; its extracts contain diterpenoids, diterpene glycosides, lactones, flavonoids, and flavonoid glycosides. Whole plant leaves and roots are also used as a folklore remedy for different diseases in Asia and Europe (49). **Therapeutic property-** AP has been reported to have a broad range of pharmacological effects including anticancer, antidiarrheal, antihepatitis, anti-HIV, antihyperglycemic, anti-inflammatory antimicrobial, antimalarial, antioxidant, cardiovascular, cytotoxic, hepatoprotective immunostimulatory. All the therapeutic bio-activities belong to AP were critically reviewed by Md. S. Hossain *et al.*, 2014. (49). **Antimalarial-** Effect of Methanolic leaf extract of *A. paniculata* was examined in P. berghei ANKA infected ICR mice, using chloroquine as a positive control. Parasitemia was then monitored, combination of chloroquine and the extract showed substantial enhancement in their antimalarial activity significantly when compared to chloroquine treatment alone. It was reported that *A. paniculata* leaf extract has potential antimalarial property and in combination with chloroquine could be an effective, alternative source of herbal antimalarial drugs (50). **Antidiabetic and antihyperlipidemic**- Andrographis paniculata (Burm. f.) Nees has shown an antidiabetic effect in type 1 DM rats. The purified extract of the plant and its active compound andrographolide showed antidiabetic and antihyperlipidemic effects in high-fructose-fat-fed rats, a model of type 2 DM rats (51). **Anti-inflammatory-** The anti-inflamatory activity was assayed by assaying their inhibitory effect on the release of tumor necrosis factor alpha (TNF-a) in the human monocyte. The inhibitory effect of andrographolide on the release of TNF-a was little affected by the quantitative variation of the non-standardised constituents (52). **Immunomodulatory-** The immunomodulatory effects of andrographolide was investigated on both innate and adaptive immune responses (53). **Antiviral- 1. Anti-SRV**- 90% Ethanolic extract of AP leaves analysed through HPLC to determine active compound andrographolide. The antiviral

activity of extract was determined by observing its ability on inhibiting virus in A549 cells transfected with simian retro virus by RT-PCR analysis. A low concentration (1ug/ml) of AP extract could stimulated lymphocytic cell proliferation about 38% compared to the control lymphocytic cell without any treatment. These antiviral and immunostimulant activities of AP extract was reported by OB Pongluran *et al.* 2015 (54). **2. Anti-HIV-** Andrographolide, a diterpene lactone of the Andrographis paniculata, displays anti-HIV activity in vitro in a cell free virus infectivity assay using TZM-bl cells. The andrographolide and its derivatives, 6 and 9, inhibited gp120-mediated cell fusion of HL2/3 cells (expressing gp120 on its surface) with TZM-bl cells (expressing CD4 and co-receptors CCR5 & CXCR4). Further, computational studies revealed that these molecules bind to the important residues of V3 loop of gp120. These results suggest that andrographolide derivatives may be promising candidates for prevention of HIV infection (55).

Momordica charantia: **Background-** *Momordica charantia* L. (*M. charantia*), a member of the *Cucurbitaceae* family, is widely distributed in tropical and subtropical regions of the world such as India, China, and lot of other countries. It has been used in folk medicine for the treatment of diabetes mellitus, and its fruit has been used as a vegetable for thousands of years. Two varieties of *M. charantia* are cultivated in India *M. Charantia* var., *charantia* with large fruits that are fusiform in shape and *M. charantia* var., *muricata* that are identified by small, round fruits (190). **Bioactive compound-** Proteins, polysaccharides, flavonoids, triterpenes, saponins, ascorbic acid, charantin, momordin and steroids have been found in this plant (56). **Therapeutic property-** Various biological activities of *M. charantia* have been reported, such as antihyperglycemic, antibacterial, antiviral, antitumor, immunomodulation, antioxidant, antidiabetic, anthelmintic, antimutagenic, antiulcer, antilipolytic, antifertility, hepatoprotective, anticancer and anti-inflammatory activities. However, both in vitro and in vivo studies have also demonstrated that *M. charantia* may also exert toxic or adverse effects under different conditions. Biological activities regarding pharmacological view as well as their adverse effects were discussed in a comprehensive manner by Shuo Jia *et al.*, 2017 (56). **Antimalarial and Antipyretic-** *Momordica charantia* was evaluated for antimalarial activities against different *Plasmodium* species. The study showed moderate *in vivo* activity of *M. Charantia* extract against rodent malaria *Plasmodium vinckei petteri* and an excellent anitimalarial activity *in vitro* on *Plasmodium falciparum* (57). The ethanolic extracts of *M. charantia* fruit (500 mg/ kg b.wt.) showed antipyretic effect in a study that was carried out using yeast-induced pyrexia in rats. The antipyretic activity of *M. charantia* was postulated to be due to individual or combined action of bioactive constituents present in it (58). **Antidiabetic and antihyperlipidemic activity-** Bitter gourd has the potential to become a component of the diet or a dietary supplement for diabetic and pre-diabetic patients owing to the presence of insulin like molecules. Recent investigations have suggested that bitter gourd extracts may ameliorate high fat diet induced obesity and hyperlipidemia in animal models. Moreover, its supplements in food result in lowering weight gain and visceral fat mass (59). MC deserves more attention as they may not only reduce hyperglycemia but also protect against the build-up of tissue advanced glycation endproducts(AGEs) and reduce oxidative stress in patients with diabetes (169). **Anti-inflammatory-** Anti-inflamatory effect of *M.* Charantia was reported in sepsis mice (60). **Immunomodulatory**- *M. charantia* methanolic extracts can significantly promote the secretion of NO and phagocytic activity evaluated via carbon clearance assays in in vivo studies (61). A water-soluble polysaccharide activated macrophages, splenocytes and thymocytes in vitro, with a maximum effect on NO production and SPI index at a concentration of 200 μg/mL, while the most effective dose to stimulate splenocytes was observed at 25 μg/mL (62). Studies have shown that after two days of incubation with a dose of 100 μg/mL, α- and β-momordicin have almost no cytotoxic effects on normal cells (63); the substances have been proven to play an immunomodulatory role by inhibiting the activity of lymphocytes or shifting the kinetic parameters of immune responses (64); they significantly inhibited mitogenic responses present in mice spleen cells due to the lectin, concanavalin A and the lipopolysaccharides. Momordicin activates and promotes B cell proliferation by inducing surface membrane immunoglobulin activity, while increasing B cell subsets CD86 (cell activation target point) expression, which plays a major role in humoral immunity. In addition, it can induce spleen cells to secrete large amounts of non-specific immunoglobulin IgM after 96 h co-culture and play a role in immune regulation (65). In vitro, saponins isolated from *M. Charantia* may promote IL-2 secretion by varying the ratio of T cells, enhancing phagocytic activity and improving immune function in aging mice (66). **Components of antiviral Activity-** Shuo Jia *et al.*, 2017 also demonstrated in his review about antiviral activity of different functional components from *M. Charantia* (56). Proteins and peptides are also the main functional components in the fruit and seeds of *M. charantia*. Many types of proteins and peptides have been isolated from different parts of *M. charantia*, such as ribosome inactivating proteins (RIPs), *Momordica charantia* lectin (MCL), Momordica anti-HIV protein of 30 kD (MAP30), α-momorcharin (α-MMC), β-momorcharin (β-MMC), γ-momorcharin, δ-momorcharin and ε-momorcharin, which possess RNA *N*-glycosidase activity, PAG activity, DNase-like activity, phospholipase activity,

superoxide dismutase activity, anti-tumour, anticancer, immunosuppressive and anti-microbial activity (67,68,69,70,71,72,73). A variety of compounds isolated from *M. charantia* have antiviral activity; many of them are proteins and steroids (76,77). RIPs are a kind of RNA glycosylases that cleave an adenine–ribose glycosidic bond; it is a type of alkaline protein, which can inhibit the process of protein synthesis by inactivating ribosomes (67,69). **Antiviral- 1. Anti-HIV-** MAP30 is the main component of antiviral activity in vitro; it selectively kills lymphocytes and macrophage infected by HIV, inhibits HIV-I virus DNA replication in monocytes, while exerting minimal cytotoxicity on uninfected cells (78). Similarly, research also found that MAP30 of bitter gourd proteins can inhibit HIV activity, depress the expression of the virus core protein p24 and viral-associated reverse transcriptase (HIV-RT), while having less effect on cellular DNA or protein synthesis in H9 cells (79). MRK29, as a lectin isolated from *M. charantia*, was found to act through inhibition of viral reverse transcriptase (80). **2. Anti-influenza-** The new antiviral activity of the protein extract from MC was determined with different subtypes of influenza A that were not only H1N1 and H3N2 but also H5N1 subtypes. The protein was of 30 kDa was purified from the seed of MC using an anion exchanger and HPLC system. As a result of the broad spectrum of its antiviral activity, this edible plant can be developed as an effective therapeutic agent against various and even new emerging subtypes of Influenza A (74). **3. Antiviral to other viruses-** Ethanolic extracts from leaves and stems of *M. charantia* highly inhibit HSV-1 and SINV viruses, and research also suggests that the antiviral activity reflects a close dependence on photosensitizer(s) rather than momordicin I or II (75). Momordicin had direct protective effect on Coxsackie virus (CVB3)-infected myocardiocyte, and depressed RNA transcription and translation of CVB3 in myocardial cells (81).

Moringa oleifera*: *Background- *Moringa olifera* Lam. is a tree that grows widely in many tropical and subtropical countries, bolongs to the family of *Moringaceae.* Its origin is in the north of India. It is grown commercially in India, Africa, South and Central America, Mexico, Hawaii, and throughout Asia and Southeast Asia. It is known as the drumstick tree based on the appearance of its immature seed pods, the horseradish tree based on the taste of ground root preparations, and the ben oil tree from seed-derived oils. In some areas, immature seed pods are eaten, while the leaves are widely used as a basic food because of their high nutrition content (82,83). *Moringa oleifera* leaves, seeds, bark, roots, sap, and flowers are widely used in traditional medicine, and the leaves and immature seed pods are used as food products in human nutrition. Leaf extracts exhibit the greatest antioxidant activity, and various safety studies in animals involving aqueous leaf extracts indicate a high degree of safety. No adverse effects were reported in association with human studies (84). Seeds, leaves, oil, sap, bark, roots, and flowers are widely used in traditional medicine. *Moringa* leaves have been characterized to contain a desirable nutritional balance, containing vitamins, minerals, amino acids, and fatty acids (83). **Bioactive compounds-** Additionally, the leaves are reported to contain various types of antioxidant compounds such as ascorbic acid, flavonoids, phenolics, and carotenoids. According to several commentaries (82,83). **Therapeutic property**- Various preparations of *M. oleifera* are used for their antiinflammatory, antihypertensive, diuretic, antimicrobial, antioxidant, antidiabetic, antihyperlipidemic, antineoplastic, antipyretic, antiulcer, cardioprotectant, and hepatoprotectant activities are reviewed by Sidney J. Stohs et al 2015 (84) . Also their nutritional content as well as antioxidant and antimicrobial characteristics are discussed. No adverse effects were reported in any of the human studies that have been conducted to that date (84). **Antimalarial-** The emergence and spread of antimalarial drug resistance of *Plasmodium* parasites, as well as hypoglycemia, during malaria infection, and subsequent death, are critical problems in malaria-endemic areas. Hence, finding new compounds, especially plant extracts having antimalarial and anti-hypoglycemic activities, are urgently needed. The study aimed to investigate the antimalarial and anti-hypoglycemic effects of *Moringa oleifera* leaf extract in *Plasmodium berghei* infection in mice. Aqueous crude extract of *M. oleifera* leaves was freshly prepared and used for an efficacy test *in vivo*. The aqueous crude extract of *M. oleifera* leaves exerted antimalarial and anti hypoglycemic effects in *P. berghei* infection in mice (85). **Antidiabetic and antihyperlipidemic**- The therapeutic potential of *M. oleifera* leaves in treating hyperglycemia and dyslipidemia was reviewed by Mbikay *et al.*, 2012 (82). **Anti-inflammatory-** Moringa oleifera, an herbal plant has been claimed to be effective in the treatment of various types of inflammatory conditions. However, there is lack of scientific studies to ratify these claims. Therefore, the present study was undertaken to explore the anti-inflammatory activity of aqueous extract of leaves of Moringa oleifera (AEMO) in experimentally induced inflammation in albino rats (86). **Immunomodulatory-** Immunomodulatory effect of ethanolic extract (50%) of *M. oleifera* leaves (MOE) has been studied in normal and immunosuppressed mice models. Effect of MOE on phagocytic activity of mice macrophages was determined by carbon clearance test. MOE showed significant dose dependent increase in WBC, percent neutrophils, weight of thymus and spleen along with phagocytic index in normal and immunosuppressed mice. The results indicate that MOE significantly reduced cyclophosphamide induced

immunosuppression by stimulating both cellular and humoral immunity (87). **Antiviral-** Antiviral activity of MO against viruses like HIV, HSV, HBV, EBV, FMDV and NDV was reviewed by D. Biswas *et al.* 2019 (88). Niaziminin is one of the thiocarbamate compounds present in MO leaves that had considerable antiviral activity against Epstein Barr (RNA virus) (89). Aqeous extract of MO leaves showed protective role against Hepatitis B virus(HBV), genotypes C and H transiently transfected Huh7 cells (90).

***Curcuma longa*: Background-** *Curcuma longa* L., a plant belongs to Zingiberaceae family native to the Indian Subcontinent and Southeast Asia (Wikipedia.org). Its rhizome used as spice with the common name of turmeric, in India called Haridra. *C. Longa* rhizome consist of a polyphenol called curcumin which is the major ingradient of turmeric. As many other plant materials, there are differences in the curcumin content for the *Curcuma longa* from different geographical regions and it could be due to hybridization with other *Curcuma* longa. The rhizome has been traditionally used as antimicrobial agent as well as an insect repellant (91). Curcumin is being recognized and used worldwide in many different forms for multiple potential health benefits. For example, in India, turmeric—containing curcumin—has been used in curries; in Japan, it is served in tea; in Thailand, it is used in cosmetics; in China, it is used as a colorant; in Korea, it is served in drinks; in Malaysia, it is used as an antiseptic; in Pakistan, it is used as an anti-inflammatory agent; and in the United States, it is used in mustard sauce, cheese, butter, and chips, as a preservative and a coloring agent, in addition to capsules and powder forms. Curcumin have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized As Safe" (GRAS) (92). The old Hindu texts have described that turmeric is as aromatic stimulant and carminative. Recently powder of turmeric used as traditional medicine against gastrointestinal diseases, especially for biliary and hepatic disorder, diabetic wounds, rheumatism, inflammation, sinusitis, anorexia, coryza and cough (93). **Therapeutic property-** Turmeric which act as anticancer, anti-diabetic, antioxidant, hypolipidemic, anti-inflammatory, antimicrobial, anti-fertility (93). **Bioactive compounds-** Curcumin or diferuloylmethane with chemical formula of (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) and other curcuminoids constitute the main phytochemicals of *Curcuma longa* L. (Zingiberaceae family) rhizome with the common name of turmeric. This polyphenolic compound due to a variety of biological activities has been gained significant attention of researches all over the world. Turmeric, an ancient coloring spice of Asia, as the main source of curcumin is traditionally used for many remedies. curcumin due to a variety of specific characterizations is in interest of scientists in recent years (91). **Antimalarial-** Curcumin, a bioactive compound in Curcuma longa, exhibits antimalarial effects. In silico docking simulation studies suggest that curcumin possesses glycogen synthase kinase-3β (GSK3β)-inhibitory properties. The *in vivo* study demonstrated that the antimalarial action of curcumin involved inhibition of GSK3β (94). **Antidiabetic-** Curcumin possesses antidiabetic effects and mitigates advanced glycation end products induced complications of diabetes (95). **Antihyperlipidemic-** Ethanolic extract of *C. Longa* administered orally to obese wister albino rats and their serum lipid profile (total chelesterol, TG and LDL levels were significantly declined but HDL level was not altered, comparing control. *Curcuma longa* Linn. had a hypolipidemic effect (96). **Anti-inflammatory/antiarthritic-** Curcuma longa (CL) or turmeric is an Ayurvedic herb that has been traditionally used to treat inflammatory conditions like rheumatoid arthritis (RA). Collagen-induced arthritis (CIA) is a well established experimental auto-immune mediated polyarthritis in susceptible strains of rodents. The administration of CL extract arrested the degenerative changes in the bone and joints of collagen induced arthritis (97). **Immunomodulatory-** A water extract of Curcuma longa (L.) [vern. Turmeric] roots (TurmericImmune™) standardized for a minimum 20 % of turmeric polysaccharides (TurP) ukonan A, B, C and D was evaluated for its biological properties in vitro tissue culture studies. Results the water extract of TurP exhibited induced-nitric oxide (NO) production in RAW264.7 macrophages. These results suggested the immunomodulatory effects of TurP (98). **Antiviral activities of *Curcuma longa* L. and curcumin-** Soheil Zorofchian Moghadamtousi et al., 2014 elaborately described in his review on antiviral activity of curcumin (91). **1. Anti-HIV-** Viral long terminal repeat (LTR) has a critical role in transcription of type 1 human immunodeficiency virus (HIV-1). Inhibition of LTR activity can be a possible pathway for antiviral drug candidates in order to block HIV-1 replication (99,100). Curcumin proved to be an effective compound to inhibit the HIV-1 LTR-directed gene expression without any major effects on cell viability (101). Curcumin and its derivatives, namely, reduced curcumin, allyl-curcumin, and tocopheryl-curcumin, revealed 70% to 85% inhibition in Tat protein transactivation of HIV-1 LTR measured by *β*-galactosidase activities of HeLa cells which in HIV-1 LTR was fused to the indictor of *lacZ*gene. Tocopheryl-curcumin demonstrated the most inhibition activity with 70% inhibition at 1 nM compared to 35% inhibition of curcumin at this concentration (102). In addition, curcumin inhibited the acetylation of Tat protein of HIV significantly by p300 associated with suppression of HIV-1 multiplication. Curcumin by targeting the acetyltransferase proteins of p300/CREB-binding protein (CBP) can be a potent compound for combinatorial HIV therapeutics (103). Curcumin was

found to be an inhibitor of HIV-1 and HIV-2 protease with IC_{50} of 100 μM and 250 μM, respectively. The curcumin boron complexes exhibited noteworthy inhibition reduced to the IC_{50} value of 6 μM with time-dependent activity. The elevated affinity of boron derivatives of curcumin is possibly associated with the attachment of the orthogonal domains of the compound in intersecting sites within the substrate-binding cavity of the protease(104). Integrase as another essential enzyme for HIV-1 replication was found to be inhibited by curcumin with IC_{50} value of 40 μM. Inhibition of deletion mutant of integrase containing only amino acids 50–212 indicated that curcumin possibly interacts with catalytic core of the enzyme. The study of energy minimization and the structural analogs of curcumin elicited that an intramolecular stacking of two phenyl rings of curcumin is possibly responsible for anti-integrase activity via bringing the hydroxyl groups into close proximity (105). However, rosmarinic acid and dicaffeoyl methane as two curcumin analogs showed noteworthy inhibitory activity against integrase of HIV-1 with IC_{50} values less than 10 μM with the slow rate of binding to the enzyme assessed by kinetic studies (106). However, through a clinical trial investigation on curcumin as an anti-HIV compound in 40 patients in eight weeks it was shown that there is no reduction in viral load or elevation in CD4 counts. But patients claimed that they preferred to take the curcumin in order to tolerate the minor gastrointestinal sufferings and feel better (107). This demonstrated that clinical trials can possibly show up with the results completely different from *in vitro* studies. The clinical trial of clear liquid soap containing 0.5% w/v ethanol extract of *C. longa* rhizome on HIV patients reduced the wound infections and 100% decrease in itching symptom and it also affected the abscess to convert to dryness scabs (78.6%) within 2 weeks (108). **2. Anti-influenza-** Curcumin showed the anti-influenza activity against influenza viruses PR8, H1N1, and H6N1. The results showed more than 90% reduction in virus yield in cell culture using 30 μM of curcumin. The plaque reduction test elicited the approximate EC_{50} of 0.47 μM for curcumin against influenza viruses (109). In H1N1 and also H6N1 subtypes, the inhibition of haemagglutinin interaction reflected the direct effect of curcumin on infectivity of viral particles and this has proved by time of drug addiction experiment. Additionally, unlike amantadine, viruses developed no resistance to curcumin. The methoxyl derivatives of curcumin also did not show noteworthy role in the haemagglutination (109). These results proved the significant potential of curcumin for inhibition of influenza. **3. Antiviral to other viruses-** *In vitro* study of curcumin and its derivatives, namely, gallium-curcumin and Cu-curcumin, exhibited remarkable antiviral activity against herpes simplex virus type 1 (HSV-1) in cell culture with IC_{50} values of 33.0 microg/mL, 13.9 microg/mL, and 23.1 microg/mL, respectively. The 50% cytotoxic concentration (CC_{50}) of the respective compounds on Vero cell line showed to be 484.2 μg/mL, 255.8 μg/mL, and 326.6 μg/mL, respectively (110). Curcumin considerably decreased the immediate early (IE) gene expression and infectivity of HSV-1 in cell culture assays. Curcumin has an effect on recruitment of RNA polymerase II to IE gene promoters through mediation of viral transactivator protein VP16, by an independent process of p300/CBP histone acetyl transferase effect (111). *In vitro* replication of HSV-2 could be decreased by curcumin with ED_{50} value of 0.32 mg/mL (111). Moreover, an *in vivo* study on mouse model with intravaginal HSV-2 challenge showed significant protection against HSV-2 infection due to administration of curcumin. This study showed that curcumin can be a good candidate for developing the antiviral products used intravaginally by women for protection against sexually transmitted herpes virus infection (112). Indeed, a metallo-herbal complex of curcumin with copper (Cu^{2+}) demonstrated microbicidal effect for further studies of vaginal gel with antiviral activity (113). Coxsackieviruses cause a variety of diseases such as dilated cardiomyopathy and myocarditis. Coxsackievirus B3 (CVB3) in spite of extensive investigations is still a major human pathogen without specific effective and approved treatment (114,115). Curcumin exhibited the antiviral activity against coxsackievirus by reduction of viral RNA expression, protein synthesis, and virus titer. In addition, it was found to have a protective effect on cells against virus-induced apoptosis and cytopathic activity. Analysis of different pathways showed that curcumin forced its potent antiviral effect in inhibition of coxsackievirus replication through dysregulation of the ubiquitin-proteasome system (UPS) (116). The recent studies proved that the UPS-mediated protein modification or degradation is an essential factor in the regulation of coxsackievirus replication (117). Liver diseases associated with viral infections are major pandemics (118). The fact that hepatitis B virus (HBV) elevates the possibility for the hepatocellular carcinoma (HCC) development some 100-fold and 695900 deaths occurred due to liver cirrhosis and HCC worldwide in 2008 makes the need to find new antivirals against hepatitis viruses (119,120). The study of antiviral effect of aqueous extract of *Curcuma longa* rhizoma against HBV in HepG 2.2.15 cells containing HBV genomes showed repression of HBsAg secretion from liver cells without any cytotoxic effect. It also suppressed the HBV particles production and the rate of mRNA production of HBV on infected cells. The*Curcuma longa* extract suppressed HBV replication by increasing the rate of p53 protein through enhancing the stability of the protein as well as transactivating the transcription of p53 gene. It was understood that the extract has suppressed HBV enhancer I and X promoter leading to repression of HBx gene transcription by affecting p53 (121). *In vitro* investigation of the antiviral activity of curcumin Huh7 replicon cells expressing the hepatitis C virus (HCV) indicated that curcumin can be a potent

anti-HCV compound. Results showed the decrease in HCV gene expression and replication through suppressing the Akt-SREBP-1 pathway. In addition, the mixture of curcumin and IFNα as the known anti-HCV therapy induced profound inhibitory activity on HCV replication and demonstrated that curcumin can be possibly used as a complementary therapy for HCV (122). High-risk human papillomaviruses (HPVs) infection via the expression of E6 and E7 viral oncoproteins has a critical role for development of cervical carcinoma. Curcumin showed the inhibitory activity against the expression of E6 and E7 genes of HPV-16 and HPV-18 as two main highly oncogenic human papilloma viruses (123). The transcription factor AP-1 is a critical factor for transcriptional regulation of high-risk HPVs such as HPV-16 and HPV-18. Curcumin downregulates the AP-1 binding activity in HeLa cells with decreasing effect on the transcription of HPV-18 (124). The results showed that curcumin through apoptosis modulation and also prevention of NFκB and AP-1 translocation associated with downregulation of viral oncogenes and decreasing the transcription of HPVs can be a good candidate for the management of highly oncogenic HPV infections (123,124). Japanese encephalitis virus (JEV) as an important endemic arbovirus in Southeast Asia is a major cause of acute encephalopathy which generally affects the children and leads to death in one third of patients. The permanent neuropsychiatric sequel is a complication for many survivors from JEV due to ineffective therapeutic measure (125). The investigation of antiviral activity of curcumin on Neuro2a cell line infected with JEV showed reduction in production of infectious viral particles through inhibition of ubiquitin-proteasome system. The results of *in vitro* study indicated that curcumin through modulating cellular levels of stress-related proteins, reducing proapoptotic signaling molecules, restoration of cellular membrane integrity, and reduction in reactive oxygen species in cellular level imparts neuroprotection and can be a potential for further investigations (126). Oncogenesis by human T-cell leukemia virus type 1 as an etiologic factor of adult T-cell leukemia (ATL) is critically dependent on the activation of the activator protein 1 (AP-1) (127). The DNA binding and transcriptional effect of AP-1 in HTLV-1-infected T-cell lines were suppressed by curcumin treatment. Curcumin also inhibited the expression of JunD protein as an important factor in AP-1-DNA complex in HTLV-1-infected T-cells as well as HTLV-1 Tax-induced AP-1 transcriptional effect. Cell cycle arrest and inducing of apoptosis were found to be possible mechanisms against HTLV-1 replication in infected T-cell line by curcumin. Suppression of AP-1 activity possibly through decreasing the expression of JunD protein is introduced as a possible pathway for anti-ATL activity of curcumin (128).

***Nigella sativa*: Background-** *Nigella sativa* L. (also known as black cumin, nigella, kalojeera, or kalonji) is an annual herb in the family Ranunculaceae, native to a large region of the Indian Subcontinent, West Asia, eastern Mediterranian and northern Africa. Black seed or black cumin, the fruit of NS which is used as spice (129) with many pharmacological properties. Among its many active constituents, thymoquinone (TQ) is the most abundant constituent of the volatile oil of *Nigella sativa* (*N. sativa*) seeds. It is an annual herb. The use of *N. sativa*(NS) seeds and oil in traditional remedies goes back more than 2000 years, and the herb is described as 'the Melanthion' by Hippocrates and Discroides, Black seeds and their oil have a long history of folklore usage in the Indian and the Arabian civilizations as food and medicine and have been commonly used as treatment for a variety of health conditions pertaining to the respiratory system, digestive tract, kidney and liver functions, cardiovascular system, and immune system support, as well as for general well-being (130). **Bioactive compounds-** contains many active components, such as thymoquinone (TQ), alkaloids (nigellicines and nigelledine), saponins (alpha-hederin), flavonoids, proteins, fatty acids, and many others, that have positive effects in the treatment of patients with different diseases. TQ is the most abundant constituent in the volatile oil of NS seeds, and most of the herb's properties are attributed to it (130). **Therapeutic property-** Cell culture studies and animal models have indicated several therapeutic potentials, such as anti-cancer, antimicrobial, analgesic, antipyretic, contraceptive and anti-fertility, anti-oxytocic, anti-tussive, anti-inflammatory, and anti-oxidant, potentials, for black seed and its active component TQ. NS or TQ anticancer activity has been demonstrated for blood, breast, colon, pancreatic, liver, lung, fibrosarcoma, prostate, and cervix cancer cell lines and in animal models of lung, kidney, skin, colon, and breast cancer. Black seed's antimicrobial effects include those on gram-negative and gram-positive bacteria, viruses, and parasites. NS was also found to be able to relieve the symptoms of or cure patients with several diseases, such as hypertension, dyslipidemia, metabolic syndrome, diabetes, asthma, convulsion and natural and chemical toxicities. NS and TQ utilization could prevent many disorders including neurobehavioral, kidney and liver disorders, different diseases and morbidity conditions in humans (130). **Antimalarial-** The antimalarial and antioxidant activities of methanolic extract of Nigella sativa seeds (MENS) were investigated against established malaria infection in vivo using Swiss albino mice. The antimalarial activity of the extract against Plasmodium yoelli nigeriensis (P. yoelli) was assessed using the Rane test procedure. Chloroquine (CQ)-treated group served as positive control. The extract, at a dose of 1.25 g/kg body weight significantly suppressed P. yoelli infection in the mice by 94%, while CQ,

the reference drug, produced 86% suppression when compared to the untreated group after the fifth day of treatment (131). **Antidiabetic and anti-hyperlipidemic activity-** NS (Nigella sativa) L. Seed hydroalcholic Extract was studied to determine hypoglycemic and hypolipidemic effect in Streptozotocin- induced diabetic rats. It was observed that NS (Nigella sativa) has a potential hypoglycemic effect as it signifcantly decrease blood glucose level compared to control group. The SGPT, SGOT and CRP were also decreased signifcantly. Therefore NS (Nigella sativa) might be effective against liver malfunction. An indicative antilipidemic effect was also observed as TC, TG, LDL, VLDL showed significant decrease whereas HDL showed significant increase by NS (Nigella sativa) treatment compared to diabetic group. These results showed that hydroalcholic extract of NS (Nigella sativa) at low doses has hypoglycemic as well as hypolipidemic effects in diabetic subjects. (132). **Anti-inflammatory –** *Nigella sativa* acts as anti-inflamatory agent in asthma. (133). **Antiarthritic**-Thymoquinone attenuates rheumatoid arthritis by downregulating TLR2, TLR4, TNF-α, IL-1, and NFκB expression levels (134). **Immunomodulatory-** *N. sativa* improves the action of antioxidant enzymes (catalase, glutathione peroxidase, and glutathione-S-transferase) and acts as a free radical scavenger. As an anti-cancer agent, its modulatory activity on molecular targets, including p53, p73, PTEN, STAT3, PPAR-g, activation of caspases, and generation of ROS had been demonstrated. As an anti-inflammatory and immunomodulatory agent, it suppresses inflammatory mediators, leukotrienes, prostaglandins, and B cell-mediated immune response while it balances Th1/Th2 ratio and potentiates T cell and natural killer cell-mediated immune response (135). **Antiviral- 1. Anti-HIV-** *Nigella sativa* had been documented to possess many therapeutic functions in medicine but the least expected is sero-reversion in HIV infection which is very rare despite extensive therapy with highly active anti-retroviral therapy (HAART). This case presentation is to highlight the complete recovery and sero-reversion of adult HIV patient after treatment with *Nigella sativa concoction* for the period of six months (136). **Anti-COVID-19-** Two new probable inhibitors of COVID-19 by molecules from *Nigella sativa L*, which is highly reputed healing herb in North African societies and both Islamic and Christian traditions. The discovery of the M^{pro}protease structure in COVID-19 provides a great opportunity to identify potential drug candidates for treatment. Focusing on the main proteases in CoVs ($3CL^{pro}$/M^{pro}) (PDB ID 6LU7 and 2GTB); docking of compounds from *Nigella Sativa* and drugs under clinical test was performed using Molecular Operating Environment software (MOE). Nigellidine docked into 6LU7 active site gives energy complex about -6.29734373 Kcal/mol which is close to the energy score given by chloroquine (-6.2930522 Kcal/mol) and better than energy score given by hydroxychloroquine (-5.57386112 Kcal/mol) and favipiravir (-4.23310471 kcal/mol). Docking into 2GTB active site showed that α- Hederin gives energy score about-6.50204802 kcal/mol whcih is better energy score given by chloroquine (-6.20844936 kcal/mol), hydroxychloroquine (-5.51465893 kcal/mol)) and favipiravir (-4.12183571kcal/mol). Nigellidine and α- Hederin appeared to have the best potential to act as COVID-19 treatment (137).

Antihelmintic activity of some Indian traditional bitter plants/spices (SITBP/S):

Azadirachta* indica-**The aqueous extract of Azadirachta Indica Leaves was investigated for anthelmintic activity using earthworms (Pheretima posthuma), tapeworms (Raillietina spiralis) and roundworms Therefore, the anthelmintic activity of the aqueous extract of Azadirachta Indica Leaves has been reported (138). ***Andrographis paniculata- Methanolic and aqeous extracts of AP leaves exhibited significant anthelmintic activity in vitro. (139). ***Momordica charantia-*** Methanol extract of *M. Charantia* of fruit peel showed potent anthelmintic effect which is similar to standard albendazole. Whole fruit and seed extract also produced significant anthelmintic effect. Whole fruit juice and peel juice showed similar but moderate *in vitro* anthelmintic effect (140). **larvicidal activity**-*Momordica charantia* has shown good larvicidal activity against three breeding mosquito species: *Anopheles stephensi*, *Culex quinquefasciatus* and *Aedes aegypti* (141). ***Moringa oleifera-*** Seed extracts of *M. Oleifera* were reported as anthelminthic (142). ***Curcuma longa-*** The rhizome extract of CL exhibited potent anthelmintic efficacy against the nematode parasite, *Haemonchus* spp (143). ***Nigella sativa-*** The black seeds (*N. sativa*) ethanolic extract had antihelminthic effect against *A. suum*. The black seeds ethanolic extract had LC50 at concentration of 1,693% (144).

Antiulcer activity of some Indian traditional bitter plants/spices (SITBP/S):

Azadirachta indica- Aqueous neem leaves extract produce highly potent antiulcer activity (145). *Azadirachta indica*, an evergreen tree, is used by several folkloric practitioners to treat peptic ulcers in India. The leaves of *A. Indica* possess antiulcer activity and possibly act via multiple mechanisms including inhibition of the histamine-2 receptors/H^+-K^+-ATPase, prostaglandin modulation, or antioxidation, that confirms the folkloric claim of *A. indica* being effective in

the treatment of peptic ulcer diseases (146). ***Andrographis paniculata-*** Antiulcer activity of *Andrographis paniculata* was evaluated by cysteamine induced duodenal ulcer model in rats. Hydroalcoholic extact of *Andrographis paniculata* showed the ulcer preventing effect due may be its mucin preserving and antioxidant nature (147). ***Motoric charantia-*** *Momordica charantia* L. (Cucurbitaceae) commonly known as 'bitter gourd' is a multi purpose herb cultivated in different parts of the world for its edible fruits. The effect of standardized methanolic extract of *Momordica charantia* L. fruits on gastric and duodenal ulcers was evaluated (148). ***Moringa oleifera-*** The methanol fraction of *M. oleifera* leaf extract was found to possess significant protective actions in acetylsalicylic acid, serotonin and indomethacin induced gastric lesions in experimental rats. A significant enhancement of the healing process in acetic acid—induced chronic gastric lesions was also observed with the extract-treated animals (149). ***Curcuma longa-*** Effect of *Curcuma longa* revealed significant antiulcer activity (150). ***Nigella sativa-*** An aqueous suspension of Black seed significantly prevented gastric ulcer formation induced by necrotizing agents. It also significantly ameliorated the ulcer severity. The anti-ulcer effect of NS against induced gastropathies is possibly prostaglandin-mediated and/or through its antioxidant and anti-secretory activities (151).

Taste of some Indian traditional plants/spices:

Azadirachta indica- Bitterness of neem leaf was described by Abhinandya Datta *et al.* 2017 (152). ***Andrographis paniculata-*** *Andrographis Herba* (AH), the dry aerial segments of *Andrographis paniculata* (Burm.f.) Nees, is a common herbal remedy with bitter properties in traditional Chinese medicine (TCM) theory. Although bitterness is one of the features representing Chinese medicine, it has not been implemented as an index to assess the quality and efficacy of TCM because of peoples' subjectivity to taste. Bitterness of AH was quantified by electronic tongue technology (153). ***Momodica charantia-*** All parts of the plant, including the fruit taste very bitter as its contains a bitter compound called momordicine (154). ***Moringa oleifera-*** The slightly bitter taste of *M. Oleifera* is due to presence of glycosinolates (155). ***Curcuma longa-*** Turmeric is the dried root/rhizome of the plant *C. longa* has pungent bitter smell and bitter taste (156). The warm and bitter taste of the spice adds a unique flavor to the curries and is a common condiment in an Indian kitchen (157). ***Nigella sativa-*** *N. sativa* has pungent bitter taste (129).

Safety concern of consuming some Indian traditional bitter plants/spices (SITBP/S):

Azadirachta indica- Neem is POSSIBLY SAFE for most adults when taken by mouth for up to 10 weeks, when applied inside the mouth for up to 6 weeks, or when applied to the skin for up to 2 weeks. When neem is taken in large doses or for long periods of time, it is POSSIBLY UNSAFE. It might harm the kidneys and liver (158). Special Precautions and Warnings- Children: Taking neem seeds or oil by mouth is LIKELY UNSAFE for children. Serious side effects in infants and small children can happen within hours after taking neem oil. These serious side effects include vomiting, diarrhea, drowsiness, blood disorders, seizures, loss of consciousness, coma, brain disorders, and death (158). Pregnancy and breast-feeding- Neem oil and neem bark are LIKELY UNSAFE when taken by mouth during pregnancy. They can cause a miscarriage (158). **Antifertility**- Avoids pregnancy and neem could be used as a way of contraception (159). Organ transplant- There is a concern that neem might decrease the effectiveness of medications that are used to prevent organ rejection. Do not use neem if you have had an organ transplant (158). ***Andrographis paniculata-*** Andrographis is LIKELY SAFE when taken by mouth appropriately, short-term. It also appears to be safe when taken as a specific combination product containing andrographis extract and Siberian ginseng (Kan Jang, Swedish Herbal Institute) for up to 3 months. *Andrographis* can cause side effects such as loss of appetite, diarrhea, vomiting, rash, headache, runny nose, and fatigue. When used in high doses or long-term, andrographis might cause swollen lymph glands, serious allergic reactions, elevations of liver enzymes, and other side effects. Special Precautions and Warnings- Infants and children: Andrographis is POSSIBLY SAFE in children when taken by mouth, short-term. Andrographis has been used in combination with other herbs for up to one month. Pregnancy and breast-feeding- Andrographis is POSSIBLY UNSAFE when taken by mouth during pregnancy. There is a concern that it might cause miscarriages. Not enough is known about the safety of andrographis during breast-feeding. Stay on the safe side, and avoid using andrographis if you are pregnant or breast-feeding (160). ***Momordica charantia-*** Two abortifacient proteins, alpha- and beta-momorcharin, have been purified from the seeds of the bitter melon (*Momordica charantia*). It was found that non-cytotoxic concentrations of these plant proteins can significantly inhibit the mitogenic responses of mouse splenocytes to concanavalin A, phytohaemagglutinin and lipopolysaccharide in a dose-dependent manner (71). Bitter melon (*Momordica charantia*) is an alternative therapy that has primarily been used for lowering blood glucose levels in patients with diabetes mellitus. Four clinical trials found bitter melon juice, fruit, and dried powder to have a moderate hypoglycemic effect. These studies were small and were not randomized or double-blind,

however. Reported adverse effects of bitter melon include hypoglycemic coma and convulsions in children, reduced fertility in mice, a favism-like syndrome, increases in gamma-glutamyltransferase and alkaline phosphatase levels in animals, and headaches. Bitter melon may have additive effects when taken with other glucose-lowering agents. Adequately powered, randomized, placebo-controlled trials are needed to properly assess safety and efficacy before bitter melon can be routinely recommended. Bitter melon may have hypoglycemic effects, but data are not sufficient to recommend its use in the absence of careful supervision and monitoring (77). ***Moringa oleifera-*** While the leaves are perfectly safe, consuming large quantities of the bark or pulp may be harmful. The side effects of consuming moringa may include: 1. Lower blood pressure and slow heart rate because of the alkaloids in the plant, 2. Uterine contractions from moringa bark, 3. Cell mutations caused by a chemical isolated from roasted moringa seeds, 4. Interference with fertility. MO leaves also increased the risk of liver and kidney damage in rats. Do not consume moringa if you are pregnant, taking the diabetes drug Januvia (sitagliptin) or taking drugs that are substrates of the cytochrome P450 family of enzymes (161). ***Curcuma longa-*** 5 Side-Effects of Turmeric (Haldi)- Turmeric or haldi is an ancient root that has long been known for its medicinal and healing properties. The active ingredient in turmeric called curcumin is known to be a healthy compound that makes this spice a *desi* superfood. According to the book Healing Foods by DK Publishing, curcumin in haldi is a well-researched antioxidant and powerful anti-inflammatory that helps to fight disease-causing free radicals. However, as it is rightly advised, excess of anything can be bad and can take a toll on health. There are some side effects of turmeric that must be aware of (157). How much turmeric (haldi) per day one should consume? It is usually recommended to have about a teaspoon a day which is considered to be safe. Anything in excess may trigger certain reactions. According to Consultant Nutritionist Dr. Rupali Dutta, "Although consuming turmeric or haldi in its natural form promotes health, but excess of it can cause an upset stomach, nausea and dizziness. Especially, if a person take turmeric capsules or supplements in high amounts, it can prove to be detrimental to health. She recommend to take turmeric in its natural form in a moderate quantities to attain its health benefits. While the positive aspects of turmeric may outweigh the side effects, it is important to know that a natural healer like turmeric may cause certain health problems in the body. Here are five side effects of turmeric worth knowing (157). 1. Upset stomach- Turmeric or haldi is known to heat your body and cause inflammation in your stomach that may lead to abdominal pain and cramps. 2. Risk of developing kidney stones- Turmeric contains oxalates that may increase the risk of developing kidney stones. These oxalates bind the calcium to form insoluble calcium oxalate that is a primary cause of kidney stones. 3. May cause nausea and diarrhea- Curcumin, the active compound found in turmeric, has a tendency to trouble the gastrointestinal tract, which causes diarrhea and nausea with excess consumption. 4. May cause an allergic reaction- You may be allergic to certain compounds present in turmeric which can cause rashes, outbreaks and even shortness of breath. Allergic reactions can occur from both ingestion and skin contact. 5. Iron deficiency- Excess turmeric consumption may inhibit the absorption of iron. Therefore, people with iron deficiency should be careful not add too much turmeric in their daily meals, as it could decrease the body's ability to absorb iron (157).
Better is, obey the rule of moderation to avoid these side effects of turmeric and to enjoy its benefits (157). ***Nigella sativa-*** When taken by mouth: When taken in small quantities, such as a flavoring for foods, black seed is LIKELY SAFE for most people. Black seed oil and black seed powder are POSSIBLY SAFE when the larger amounts found in medicine are used for 3 months or less. There isn't enough reliable information to know if the amounts found in medicine are safe when used for more than 3 months. Black seed can cause allergic rashes in some people. It can also cause stomach upset, vomiting, or constipation. It might increase the risk of seizures in some people (162,163).

MATERIALS AND METHODS

Materials:

AI-/AP-/MO leaves and CL rhizome were collected from own Institute garden. MC fruit, NS seed and black pepper (*Piper nigrum*) were purchased from Bethuadahari local market. Edible ethyl alcohol (95%) purchased from medicine store, Bethuadahari. Pressure cooker (5 L)(manufactured by Hawkins), Snapdeal Cutter was purchased through online order. Bajaj Classic Mixer and Grinder, Wooden Stirer and Pure Drinking water (Purified by AquaVas filter) (20L container) (manufactured by Sutapa aqua pure) were procured from the same local market.

Methods:

Database- All the research articles and reviews were downloaded systematically using the search engine PubMed, google scholar and wider internet on CQ, HCQ and some Indian traditional bitter plants/spices. The retrieved databases were critically reviewed to hypothesise a treatment model, CBTT.

Preparation of DHF/THF/PHF formulatiom from SITBP/S, also called Institute supplied hydro alcoholic extract (ISHAE) (50%)- All herbal ingradients were taken in a 1..... :1.....ratio, as for example in case of DHF, different diherbal ingradients like leaves/fruits/rhizome from SITBP/S, according to CBTT model were chosen, collected and washed with pure drinking water, soaked with tissue paper to make it dry, weighing each herb 100g, minched into a small pieces with Snapdeal cutter and altogether pasted with a Bajaj Classic Mixer and Grinder (BCMG) (weight of the paste=100g+100g=200g in DHF). Whole mixture was taken into a pressure cooker, to the mixture 200ml (volume of water added=weight of total paste) of pure drinking water and 5g black pepper (*Piper nigrum*) powder (Previously prepared by BCMG) were added as bioavailability enhancer (177,178) and boiled until 12 whistles (whistling sound) were completed (to kill the endophytes) and cooled at room temparature followed by addition of 200ml of edible graded ethanol (95%) (volume of added alcohol=volume of added water). Whole mixture was stired for 5 minutes with a wooden stirer and filtered throuh a sterile double cheese cloth. Filtrate was thus collected into a steriled amber colored bottle, called DHF and it was considered as more/less 50% hydroalcoholic extract, where ehanol was used as an organic solvent and as well as preservative. Similarly, THF and PHF(TetHF for mild-/PenHF for moderate-/HHF for severe symptomatic patients) were prepared separately in the same way with specific ingradients, taking in an equal weight ratio (100g each) following the CBTT model. All the herbal formulations thus prepared in my Institute are called ISHAE. Similarly AALHAE (50%) and AALHAEplus (50%) were prepared separately following the same way and same protocol also.

Dosing of hydroethanolic (50%) herbal formulations [also called Institute supplied hydro alcoholic extract (ISHAE)]- 1 drop (equivalent to 20 micro litre volume) was found to be effective fòr 2 kg body weight (data not published). 1. DHF- as preventive, as for example, in case of 50kg body weight, 50÷2= 25 drops were mixed with half cup of drinking water, were drunk twice daily before meals, 2. THF – as prophylactic, similarly 1 drop/2kg body weight, thrice daily before meals, and 3. PHF(TetHF for mild-/PenHF for moderate-/HexaHF for severe symptoms) – as alternative &/curative in symptomatic patients, similarly 1drop/2 kg body weight, thrice daily before meals. Maximum period of treatment were for 1 month. Also dosing of AALHAE and AALHAEplus were followed by same way.

RESULTS

Commonly used Indian traditional bitter plants like *Azadirachta indica* A. Juss. (Indian lilac/Nimtree/Neem), *Andrographis paniculata* (Burm. f.) *Nees.*(green chirata), *Momordica charantia* Linn. (Indian karela) and *Moringa oleifera* Lam. (Drumstick/Horseradish tree) are chosen for such search. Similarly commonly used Indian bitter traditional spices like *Curcuma longa* L. (Indian Haridra) rhizome and *Nigella sativa* L. (Indian Kalojeera) seeds are chosen for such consideration. All together they are called Some Indian traditional bitter plants/spices (SITBP/S) and their biological activities like antimalarial, antidiabetic, antihyperlipidemic, anti-inflammatory/antiarthritic, immunomodulatory, etc.) utilising as herbal remedy of therapeutic importance as well as their antiviral activities were compared along with that properties which are homologous to CQ/HCQ are shown in the Table 1. Simultaneously, type, formulation, route of administration, taste, side effects and active compound from CQ/HCQ and SITBP/S are also shown in Table 2. Thus cocktail/(di-/tri-/poly) herbal formulation as preventive/prophylactic/alternative of COVID-19 treatment prepared by following the CBTT model (Figure 1.) were implimented on a small group of COVID-19 suspected symptomatic patients, results are shown in Table 3., outcome of which lead to validate the Common-base-tetra-triangular model, shown in Figure 1.

Table 1: Biological/therapeutic behavior like antimalarial, antidiabetic, antihyperlipidemic, anti-inflammatory/antiarthritic, immunomodulatory, and antiviral activity from CQ/HCQ and SITBP/S were retrieved from literature. (+)ve sign indicates presence/possession of the property.

Name of potential	Antimalarial	Antidiabetic	Anti-hyperlipidemic	Anti-inflammatory/Antiarthiritic	Immunomodulatory	Antiviral activity	Target virus
CQ	+++	+	+	+	+	+	HIV-1, SARS-CoV (2003) and SARS-CoV-2
HCQ	+++	++	+	++	+	+	HIV-1, SARS-CoV (2003) and SARS-CoV-2
AI	+	+	+	+	+	+	HSV-1, DENV-2, Coxsackievirus, Smallpox, Chicken pox, Vaccinia virus, HBV, Chikungunya and Measles virus
AP	+	+	+	+	+	+	HIV-1, SRV
MC	+	++	+	×	+	+	HIV-1, Influenza A, HSV-1, SINV, CVB3
MO	+	×	+	+	+	+	HIV, HSV, HBV, EBV, FMDV and NDV
CL	+	+	×	++	+	+	HIV-1&II and COVID-19 M^{pro}
NS	+	+	+	++	+	+	HIV and COVID-19 M^{pro}

Table 2: Type, formulation, taste, route of administration, side effects and active ingradient/compounds present in CQ/HCQ and in the naturally occurring potentials of some Indian traditional bitter plants/spices were recorded. Data were collected from research and review articles.

Name of potential	Type	Formulation	Taste	Route of administration	Side effects of short term therapy	Active compound
CQ	Synthetic	Tablet	Bitter	Orally	Adverse side effects	Chloroquine
HCQ	Synthetic	Tablet	Highly bitter	Orally	In some cases adverse side effects	Hydroxychloroquine
AI	Natural	Aqueous/Hydoalcoholic/Alcoholic extract	Bitter	Orally	No side effects	Gedunin
AP	Natural	Aqueous/Hydroalcoholic/Alcoholic extract	Bitter	Orally	No side effects	Andrographolide
MC	Natural	Aqueous/Hydroalcoholic/Alcoholic extract	Bitter	Orally	No side effects	RIPs, MAP30, MRK29
MO	Natural	Aqueous/Hydroalcoholic/Alcoholic extract	Bitter	Orally	No side effects	Niaziminin, Moringinine
CL	Natural	Aqueous/Hydroalcoholic/Alcoholic extract	Pungent bitter	Orally	No side effects	Curcumin, Demethoxycurcumin
NS	Natural	Aqueous/Hydroalcoholic/alcoholic extract	Pungent bitter	Orally	No side effects	Nigellidine, alpha Hederin and Thymoquinone

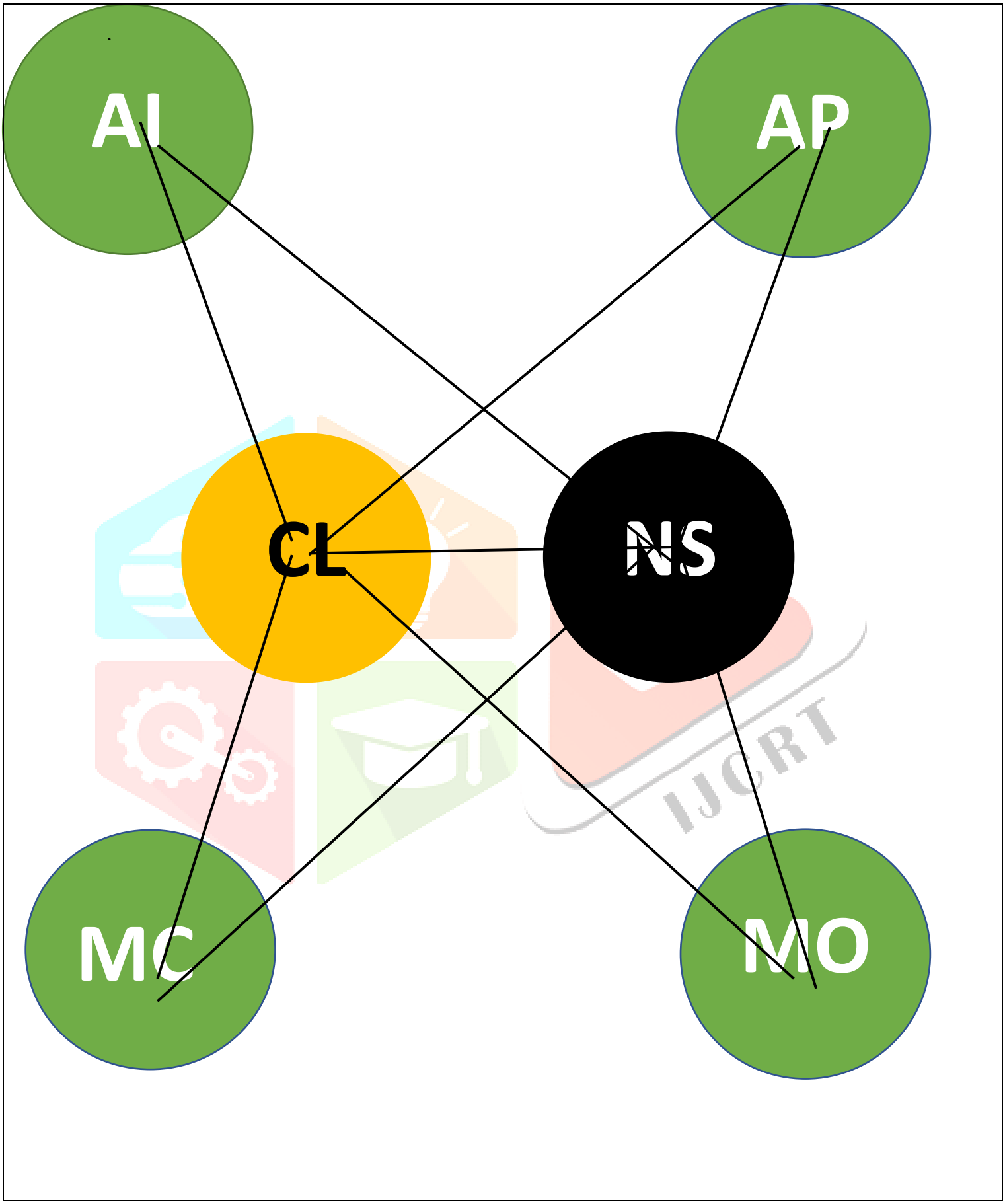

Figure1: **Common-base-tetra-triangular preventive/prophylactic or alternative treatment model of covid-19:** Any line that is composed either diherbal formulation of AI-CL or AP-CL or MC-CL or MO-CL could be used as preventive (except common base CL-NS). Remember those who are diabetic/prediabetic strictly were followed by only the couple of **MC-CL** line as preventive. Here in the present study for simplicity only **AI-CL** was chosen as preventive

for non-diabetic. Only three points triherbal formulation (trianglular combination) of **MC-CL-NS** could be (has been) used as a proper prophylactic. In case of mild symptom four point polyherbal/tetra herbal formulation like MC-CL-NS-AI or MC-CL-NS-AP or MC-CL-NS-MO could be effective. But in this study for simplicity only **MC-CL-NS-AI** was considered to prepare ISHAE for the treatment of mild symptoms. In case of moderate symptom five point polyherbal/penta herbal formulation: MC-CL-NS-AI-AP or MC-CL-NS-AI-MO could be effective, though in this study only **MC-CL-NS-AI-AP** arm was considered only for the treatment of moderate symptoms for simplicity. In case of severe symptoms six point polyherbal/hexaherbal formulation (common-base-tetra-triangular combination) of **MC-CL-NS-AI-AP-MO**, that means only the whole CBTT model thus could be effective. The preparation of ISHAE were already mentioned in the Method Section which were implimented in the present study as preventive/prophylactic and/natural curative in case of mild, moderate and severe COVID-19 suspected symptomatic patients (Warning: 1. Children, pregnant and breast-feeding women and organ transplanted/immunocompromised patients were never followed this model (71,77,158,159,160,161). 2. Diabetic patients who were under antidiabetic medication (ADM) when followed this model of treatment, blood sugar has been monitored frequently and the dose of ADM was adjusted if required, otherwise the doctor's advice were taken (77,158,160,161,162,163), staying at home isolation.

Table 3: Implimentation of different arm of CBTT model as ISHAEs as preventive/prophylactic on healthy/non-symptomatic persons and as well as altenative/curative on a small group of COVID-19 suspected symptomatic patients those who were denied to go hospital. In case of symptomatic patients, the therapy was accompanied with some specific allopathic medications like paracetamol (PCM), azithromycin(AZ) including presence/absence of antiallergic medications (AAMs=Montelukast+Levocetirizine). Feeling of unwell due to silent hypoxia was treated with *Abroma augusta* leaf hydroalcoholic extract (AALHAE) (50%) in moderate symptomatic suspected patients. Respiratory distress/shortness of breath were treated with AALHAE plus (efficacy of AALHAE was augmented by adding *Osimum sanctum* leaves, *Zingiber* officinale, black tea and *Piper nigrum*) in severe symptomatic suspected cases. Nobody was treated/self medicated with CQ/HCQ. Also their weekly report of recovery and remaining symptoms for 4 weeks were recorded over the telephone, maintaining safest social distance.

Type of implimentation	Preventive	Prophylactic	Mild Symptomatic		Moderate Symptomatc		Severe Symptomatic	
No of persons involved	20	15	2		2		2	
Patient ID no.			1	2	1	2	1	2
Symptoms	No symptom	No symptom	Low fever, Dry cough, Soar throat, Fatigue	Low fever, Dry cough, Throat pain	Fever(100-102'F), Deep cough, Bodyaches, Feeling of unwell	Fever(101-102'F), Deep cough, Fatigue, Feeling of unwell	Fever, Deep cough, Shortness of breath, Vertigo	High Fever, Cough, Respiratory distress, Confusion
ISHAE	20	15	1	1	1	1	1	1
Application of CBTT model (Chosen spc. Arm for ISHAE)	DHF(Di-herbal formulation) for non-diabetic: AI-CL, and for pre-/diabetic: MC-CL	THF (Tri-herbal formulation: MC-CL-NS)	TetHF (Tetra herbal formulation: MC-CL-NS-AI)	TetHF (Tetra herbal formulation: MC-CL-NS-AI)	PenHF(Penta herbal formulation: MC-CL-NS-AI-AP)	PenHF(Penta herbal formulation: MC-CL-NS-AI-AP)	HHF(Hexa herbal formulation: MC-CL-NS-AI-AP-MO)	HHF(Hexa herbal formulation: MC-CL-NS-AI-AP-MO)
Age range/Age (yr.)	35-65	15-70	60	56	65	70	58	81
Gender	M, F	M, F	F	M	F	M	F	F
Body weight(Kg)	60(average)	58(average)	66	74	64	68	66	58
Dose of ISHAE	DHF: 30drop, BDAC, 2month	THF: 29drop, TDAC, 2month	TetHF: 33drop,, TDAC, 7day	TetHF: 37drop, , TDAC, 14day	PenHF: 32drop, TDAC, 14day	PenHF: 34drop, TDAC, 21day	HHF: 33drop, TDAC, 28day	HHF: 29drop, TDAC, 28day

Pre-existing disease	Not considerable	Not considerable	Prediabetic, HTN	NIDDM	NIDDM, HTN	NIDDM	Asthma	NIDDM, HTN
Pretreated with	Not considererable	Not considerable	AHTNM	ADM	ADM, AHTNM	ADM	Deriphyllin	ADM, AHTNM
Allopathic medications used	Not applicable	Not applicable	PCM, AZ, AAMs	PCM, AZ, -	PCM, AZ, AAMs -	PCM, AZ,	PCM, AZ, AAMs	PCM, AZ, AAMs
Dose: PCM(650mg), tablet	-	-	1 tablet SOS	1 tablet SOS	1 tablet SOS	1 tablet SOS	1 tablet SOS	1 tablet SOS
Antacid/PPI tablet/capsule	-	-	1tablet/capsule SOS	1tablet/capsule SOS	1tablet/capsule SOS	1tablet/capsule SOS	1tablet/capsule SOS	1tablet/capsule SOS
Dose: AZ(500mg) tablet	-	-	1 tablet/day, 3-5day	1 tablet/day, 3-5day	1 tablet/day, 5-7day	1 tablet/day, 5-7day	1 tablet/day, 7-10day	1 tablet/day, 7-10day
Dose: AAMs (MLK10mg+LCZ5mg) tablet	-	-	1 tablet/day, 7day	-	1 tablet/day, 14day	-	1 tablet/day, 28day	1 tablet/day, 28day
Treatment for feeling of unwell with AALHAE	-	-	-	-	AALHAE: 32drop, TDAC, 14day	AALHAE: 34drop, TDAC, 21day	-	-
Treatment for respiratory distress with AALHAEplus	-	-	-	-	-	-	AALHAEplus: 33drop, TDAC, 28day	AALHAEplus: 29drop, TDAC, 28day
Gargling&/Vapour inhalation taken	-	-	Occasionally	Occasionally	Occasionally	Occasionally	Occasionally	Occasionally
Symptoms remaining after 1st week of treatment	-	-	-	Mild	Mild	Mild	Moderate	Moderate
Symptoms remaining after 2nd week of treatment	-	-		-	-	Mild	Mild	Mild
Symptoms remaining after 3rd week of treatment	-	-				-	Mild	Mild
Symptoms remaining after 4th week of treatment	-	-					-	-
Symptoms appeared during 2 months of treatment	No symptoms	No symptoms	-	-	-	-	-	-

DISCUSSION

SITBP/S showed anthelmintic behavior (146,147,148,149,150,151) as Anthelmintics or antihelminthics are a group of **antiparasitic drugs like ivermectin** that expel parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host (165). Whereas no antihelmintic property was found from literature in CQ/HCQ. Likely to be ivermectin (33), thus herbal formulations (HFs) from SITBP/S may be repurposed as anti-COVID-19.

SITBP/S showed antiulcer property indicating a benificial effect on gastropathy and gastric ulcer diseases (145,146,147,148,149,150,151). Thus HFs from SITBP/S might be repurposed like antihistaminic/PPI drug, famotidine. Whereas damage to existing gastric ulcer in CQ (30) and non-specific gastrointestinal effect in HCQ (31) were reported.

Taste of CQ/HCQ and SITBP/S are shown in Table 2. CQ has bitter taste (8) and HCQ has horrible bitter taste in mouth (9). AI-/ AP-/MC-/MO leaf has bitter taste (152,153,154,155) and CL rhizome/NS seed has pungent bitter taste (156,157,129). PHF from SITBP/S thus prepared as ISHAE were sum of bitterness which was greater bitter than individual herb. Although bitterness is one of the features representing traditional Chinese medicine (TCM), it has not been implemented as an index to assess the quality and efficacy of TCM because of peoples' subjectivity to taste (153).

Antimalarial effect of CQ/HCQ and SITBP/S are shown in Table 1. In the pipeline of antimalarial drug research CQ and HCQ had born after quinine and basically they are called two synthetic antimalarial drugs (11). Leaf, stem and bark extract of AI reduced P. Berghei induced parasitaemia in mice (38). Methanolic leaf extract of AP showed antimalarial effect in P. Berghei ANKA infected ICR mice. AP and CQ combination showed significant antimalarial activity than AP alone as compared with CQ control (50). MC has antimalarial activity against different Plasmodium species. Moderate *in vitro* and excellent *in vivo* antimalarial activity against *P. Falciparum* were observed (57). Ethanolic extract MC fruit has antipyretic effect on yeast induced pyrexia in rats (58). Leaf extract of MO has antimalaria and anti-hypoglycemic effect in *P. Berghei* infected mice (85). CL has antimalarial effect via inhibition of GSK3B (94). Methanolic extract of NS seed has antimalarial effect in malaria infected mice (131). Herbal formulation thus prepared from SITBP/S could be an alternative of CQ/HCQ in an antimalarial concern.

Antidiabetic activity/behavior of CQ/HCQ and SITBP/S are presented in Table 1. Established antidiabetic effect of CQ (12,13,16) and HCQ (14,15) are well known. Moreover HCQ reduces HbA1C level in a diabetic patient (17), whereas SITBP/S have been used as traditional antidiabetic as they are poseing hypoglycemic behaviors (39,51,59,82,95,132). AI reduces blood sugar and prevents adrenaline and glucose-induced hyperglycemia (39). AP has shown antidiabetic effect in type 1 DM rats and andrographolide, an active compund present in AP showed antidiabetic activity in rats of type 2 diabetic model (51). MO leaves can treat hyperglycemia (82). MC can control diabetic and pre-diabetic patients owing to have plant insulin (59). MC deserves more attention as they may not only reduce hyperglycemia but also protect against the biild up advanced glycation endproducts (AGEs) and reduce oxidative stress in patients with diabetes (169). Also CL mitigates AGEs induced diabetic complication (95). Hydroalcoholic extract of NS seed in STZ-induced diabetic rat showed significant potential hypoglycemic effect (132). Therefore, in concern of DM, herbal formulation (di-/tri-/poly-) might be alternative antidiabetic of CQ/HCQ as the herbal combination may reduce AGEs/A1C value like HCQ (17), that the hebal formulation may inhibit terminal glycosylation of ACE 2 receptor (23) through which virus binding/entry could be precluded.

Antihyperlipidemic effects in CQ/HCQ and SITBP/S are exhibited in Table 1. CQ amleorated lipoprotein metabolism (18) and HCQ decreased serum LDL (19). Significant antihyperlipidemic effect of SITBP/S were observed (40,51,59,82,96,132). AI leaf extract controls lipid profile in STZ induced diabetic rats (40). AP has antihyperlipidemic effect in NIDDM rats (51). MC has antihyperlipidemic effect in animal model (59). MO leaves can treat dyslipidemia (82). Ethanolic extract of CL significantly decreased lipid profile in obese rats without altering the HDL level (96). Hydroalcoholic extract of NS showed significant potential antilipidemic effect in STZ induced diabetic rats where HDL was increased at low dose of hydroalcoholic extract of NS (132). Herbal cocktail may potentiate the hypolipidemic effect could replace CQ/HCQ in an antilipidemic concern.

DM and HTN are associated adaptor of corona comorbidity. Therefore antidiabetic and antihypertensive therapeutic parameters of SITBP/S are very much important to consider which may attenuate the rate of such comorbidity as hyperlipidemia is prevalent in hypertension (164). in a cardiovascular complication, -cause of this association is unclear. But my opinion antihyperlipidemic effects of the same may have direct/ indirect role to down regulate the HTN as well as that may decline the ACE-2 expression or vice versa, which may control SARS-CoV-2 entry into the cells.

Presence of anti-inflammatory/antiarthritic and immunomodulatory effects in CQ /HCQ and SITBP/S are shown in Table 1. Both CQ and HCQ have antiarthritic and immunomodulatory effect (20). Neem leaf extract has anti-inflamatory, analgesic and antipyretic effects in rat (41) and activates cell mediated immune pathways (42) and affects NF-kB (43). AP has anti-inflamatory effect (52) and immunomodulatory effect on innate and adaptive immune response (53). Ethanolic extract of AP leaves inhibits SRV by stimulating lymphocytic celll proliferation about 38% (53). Anti-inflammatory effect of MC was demonstrated in sepsis mice (60). Immunomodulatory effect of MC methanolic extract promotes the secretion of NO and phagocytic activity (61). A water soluble polysaccharide of MC

activates macrophages, splenocytes and thymocytes *in vitro* (62). Momordicin activates and promotes B cell proliferation inducing surface membrane Ig activity (63,64,65) and saponin from MC fruit has significant immunomodulatory role and promotes IL-2 secretion varying T-cells ratio and enhancing phagocytic activity improving immune function in aging mice (66). Aqeous extract of leaves has anti-inflammatory effect in experimentally induced inflammation in rats (86). Immunomodulatory effect of 50% ethanolic extract of MO leaves increases in WBC and neutrophils count and reduced cyclophosphamide induced immunosuppression by stimulating cellular and humoral immunity (87). CL treat inflammatory condition like RA and CIA (97). Immunomodulatory effect of water soluble TurP induces NO production in RAW264.7 macrophages (98). NS shows anti-inflamatory effect in asthma (133). Antiarthritic effect of TQ attenuates RA by down regulating TNF-a, IL-1, NFkB expression (134). Immunomodulatory activity of NS exhibits on molecular targets, including p53, p73, PTEN, STAT3, PPAR-g, and activation of caspases (135). As an anti-inflammatory and immunomodulatory it suppress inflammatory mediators like leukotriene, prostaglandin, and potentiates T-cell and NK cell mediated immune response (135). Thus the herbal formulations either self prepared or institute supplied from SITBP/S could be preventive /prophylactic or alternative of intense side effective treatment of CQ/HCQ in immunomodulatory concern or specially the di-/triherbal formulation of CBTT model may be a potential preventive/prophylactic against nCoV.

Antiviral activity of CQ/HCQ and SITBP/S are shown in Table 1. **Anti-HIV-** Both CQ and HCQ has broad anti-HIV-1 activity (21). Andrographolide derivatives prevent HIV infection (55). MC has anti-HIV activity (78,79,80). MO inhibits HIV (88). CL inhibits HIV-I and II (99-108). Anti-HIV effect of NS is the cause of sero-reversion of adult HIV patient with HAART (136). Thus penta herbal combination (MC-CL-NS-AP-MO) of PHF could be repurposed as anti-COVID-19 like kaletra (25). **Anti-influenza-** Protein extract of MC inhibits influenza-A subtypes H1N1, H3N2 and H5N1(74). Curcumin from CL has anti-influenza activity against H1N1 and H6N1 subtypes (109). Suppliment of NS would significantly enhance immune responsiveness and suppress pathogenicity of influenza viruses (H9N2) in turkeys (179). Thus triherbal combination (MC-CL-NS) could be repurposed as anti-nCoV like antiflu drug flavipiravir (avigan) (25). **Antiviral to other viruses-** AI inhibits Fowl pox, Chickenpox, Vaccinia virus, Chikungunya, Measles virus, HBV, HSV-1, CVB-4 (44-48). AP inhibits SRV (54). Ethanolic extract of MC leaves and stem have anti-HSV-1 and anti-SINV activities (75). MC has anti-CVB3 activity also (81). MO has antiviral effect against HSV, HBV, EBV, FMDV and NDV (88). Niaziminin from MO leaves inhibits EBV, RNA virus (89). Also aqeous extract of MO leaves protects from HBV, C &H genotypes (90). CL inhibits HSV-1&2, CVB3, HBV, HCV, HPV-16 & 18, JEV and HTLV-1 (110-128). **Anti-COVID-19-** CQ and HCQ are weak bases, elevate pH of acididic intracellular organelles endosome/lysosome which is essential for membrane fusion (22). CQ exerts direct antiviral effects inhibiting pH dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses and coronaviruses (166). It is believed that SARS-CoV-2 enters cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, and that chloroquine may prevent the virus from binding to the receptor by inhibiting terminal glycosylation (23). HCQ inhibits SARS-CoV-2 infection *in vitro* (24). CQ and HCQ both inhibits SARS-CoV (2003) and SARS-CoV-2 before and after infection (10).

Active component/compounds of antiviral activity from SITBP/S are shown in Table 2. **Gedunin** is a tetranortriterpenoid isolated from the Indian neem (*Azadirachta indica*, Meliacae) and has been used for the treatment of malaria and other infectious diseases in traditional Indian medicine. It leads to cancer cell death by apoptosis through inactivation of p23 and activation of Caspase-7 (167). Most notably, heat shock protein 90 (hsp 90) emerged as a major component that enables viruses to hijack infected cells through the process of autophagy (180). Drug repositioning suggests that an inhibitor of hsp 90, gedunin might be used to treat covid-19. **Andrographolide**, a bioactive phytonutrient from AP repressed increased NOD-like receptor protein 3 (NLRP3), caspase-1, and interleukin-1B molecules which are extensively involved in the pathogenesis of SARS-CoV and SARS-CoV-2 (168). Active antiviral components/compounds like RIPs, MCL, MAP30, MMCs (67-73), proteins and steroids (76,77) were purified from MC fruits. **RIPs** are a kind of RNA glycosylases purified from MC that cleave an adenine–ribose glycosidic bond; it is a type of alkaline protein, which can inhibit the process of protein synthesis by inactivating ribosomes (67,69). Possibility is there, hijacked ribosomal machinary by SARS-CoV-2 in case of COVID-19 could be inactivated by RIPs. Also possibility is there to elevate the pH of acidic intracellular organelles endosomes/lysosomes by the alkaline protein RIP, like CQ/HCQ weak base, which is essential for membrane fusion (22), that is why RIPs could inhibit pH dependent replication of SARS-CoV-2 like CQ (166). Thus the edible MC seeds enriched with RIPs can be alternative of CQ/HCQ therapy that have pronounced side effects. Momordin I is a type I ribosome inactivating protein (Type 1 RIP), extracted and purified from seeds of the bitter melon *M. Charantia*, are toxic toward T-cell and HIV-1 infected macrophages for

use as a potential specialized treatment (170). **MAP30** of bitter gourd proteins can inhibit HIV activity, depress the expression of the virus core protein p24 and viral-associated reverse transcriptase (HIV-RT), while having less effect on cellular DNA or protein synthesis in H9 cells (79). **MRK29**, as a lectin isolated from *M. charantia*, was found to act through inhibition of viral reverse transcriptase (80). *Momordica charantia* is a rich source of chemically novel compounds and needs exhaustiue screening against new targets in future. This compilation of its phytochemical and pharmacological reports will help the researchers in dereplication and designing new investigational strategies. The biologically active cucurbitacins, momordicosides and steroidal glycosides from *M. charantia* may be one of the anti-nCoV potentials. In MC flesh important phenolic acids like catechin and epicatechin are ranged from 23.06 to 82.45 and 16.14 to 44.28 mg/100g dry material (171). Ethylacetate crude extract of MC contained apigenin-7-O-glycoside (1955.55 ng/mg) and naringenin-7-O-glycoside (181.30ng/mg) (172).Catechin have also been found in aqeous extract fraction of MC (171).The molecular docking of 6LU7 (COVID-19 M^{pro}) with native ligands like catechin, epicatechin, naringenin, apigenin-7-glucoside (enriched in *M. Charantia*) and quercetin (enriched in *Moringa oleifera* leaves) respectively showed significantly promising values comparing with standards like nelfinavir and lopinavir, appeared to have the best potential to act as inhibitors of novel corona virus (173). Depending on such unique and diversified antiviral and its insulin like antidiabetic activities of bioactive phytonutrients from MC has been selected as the best preventive along with CL in diabetic/prediabetic patients and also selected as an only prophylactic along with common base, CL-NS and MC-CL-NS triangle was selected as a common triangle in tetra-/penta-/hexa PHF to strengthen the anti-CoV efficacy in mild/moderate/severe symptomatic patients that was presented in proposed CBTT model.

In this context I can also mention that it was surprisingly found from a preliminary *in vitro* study: the aqeous crude extract of small round shaped Indian variety, *M. charantia* var. *muricata* showed more alpha amylase inhibitory effect than long shaped another Indian variety, *M. charantia* var. *charantia* (data will publish in a paper, soon). The assays were done in the Laboratory of PG Depatment of Biochemistry, OIST, Midnapore, West Bengal. In my Herbal Clinic of Chichuria Institute of Medical Sc. and Research, I found diabetic people were getting better control of blood sugar and HbA1C when aqeous/hydroalcoholic extract of *muricata* was used than that of *charantia* variety (data not published), resulting I used preferentially the Indian wild variety, *muricata* in CBTT model of the present study for the preparation of ISHAE.

MO leaves are enriched with **Moringinine**, Quercetin and Chlorogenic acid, have the higest antioxidant content in food and also has a remarkable range of medicinal use and high nutritional value (174). **Niaziminin** of MO leaves inhibits EBV (RNA virus) (89).

Curcumin from CL showed highly broad spectrum antiviral activities described before including anti-HIV-Ì & II (99-108) and anti-influenza effect (109). The molecular docking of 6LU7 (COVID-19 M^{pro}) with native ligands like **demethoxycurcumin** and curcumin from *C. Longa* showed significantly promising values comparing with standards like nelfinavir and lopinavir, appeared to have the best potential to act as inhibitors of novel corona virus (173).

Also molecular docking study of **nigellidine** and **a-hederin** from NS bind with main proteases in nCoVs ($3CL^{pro}/M^{pro}$) (PDB ID 6LU7 and 2GTB). Nigellidine docked into 6LU7 active site giving energy complex of energy score close to CQ but better than HCQ and favipiravir. Whereas a-hederin docked into 2GTB active site giving energy complex of energy score better than CQ, HCQ and favipiravir. Results were, indicating that nigellidine and a-hederin appeared to be the best potential main protease inhibitor in nCoV (137).

On the basis of Molecular docking study of active compounds from CL and NS in Table 2., and from their anti-HIV and anti-influenza activity, and their therapeutic effects from Table 1, CL and NS couple were selected as Common base (CL-NS) arm of CBTT model thus proposed. CBTT model thus hypothesised were implimented in a small group (6 persons) of COVID-19 suspected symptomatic patients and the results of implimentation are shown in Table 3. Two suspected patients were taken in each mild, moderate and severe symptomatic cases who were denied to go hospital, were treated with ISHAE, staying under home isolation and their family members were treated with THF (MC-CL-NS) as prophylactic. No symptoms were found in prophylactic treatment during 2 months. Patient no.1 of mild symptomatic recovered within 1st weak of treatment who was treated with PCM, AZ, AAMs and ISHAE (tetraherbal formulation: MC-CL-NS-AI), whereas patient no.2 of mild symptomatic showed still remaining the symptoms even after 1st week of treatment but was completely recovered showing no remaining symptoms after 2nd week of treatment who was treated with PCM, AZ, and ISHAE (tetraherbal formulation: MC-CL-NS-AI) indicating without AAMs, delaying of recovery was observed by 7 days in patient no.2, comparing with patient no.1, shown in Table 3. Patient

no.1 of moderate symptomatic patient showed mild symptoms even after 1st week of teatment but completely disappeared the symptoms by 2nd week of treatment who was treated with PCM, AZ, AAMs, ISHAE (pentaherbal formulation: MC-CL-NS-AI-AP) and AALHAE. Whereas, patient no.2 of moderate symptoms showed mild symptoms even after 1st week of treatment and still continuing the same mild symptoms even after 2nd week of treatment respectively, but was completely cured after 3rd week of treatment who was treated with PCM, AZ, ISHAE (pentaherbal formulation: MC-CL-NS-AI-AP) and AALHAE, indicating that without AAMs delaying the recovery by 7 days observed in patient no.2, when compared with patient no.1. as control, shown in Table 3. On the other hand faster recovery of patient no.1 in mild and patient no.1 in moderate symptomatic cases were observed by 7 days when treated with AAMs, comparing with patient no.2 of mild and patient no.2 of moderate symptomatic patients respectively as true controls. Both the patient no.1 and patient no.2 of severe symptomatic showed moderate symptoms after followed by 1st week of treatment and also both the patients showed mild symptoms even after 2nd and 3rd week of treatments respectively, but no remaining symptoms were found after 4th week of treatment, indicating that they were completely recovered and both were treated with PCM, AZ, AAMs, ISHAE (hexaherbal formulation: MC-CL-NS-AI-AP-MO) and AALHAEplus systemitically following the medical guidelines, shown in Table 3. It is pertinent to say that in case of suspected severe symptoms no risks were taken to treat without AAMs to get a true control. Also those who were treated with DHF as preventive did not show any symptom during 2 months of treatment. Thus implimentation results from the Table 3, might prove the validity of CBTT model partly. However, it needs more proper further implimentation as well as need to confirm the patients who were implimented in this study whether their influenza like illness(ILI) in mild and moderate and respiratory distress in severe symptomatic patients, treated with CBTT model +/- AALHAE/AALHAEplus and specific allopathic medications including +/- AAMs were nCoV-iduced or not.

It is relevant to say in the study that the *Piper nigrum* (black pepper) were added in the herbal formulations (ISHAEs) as piperine a major active compound from *P. Nigrum*, known as inhibitor of hepatic and intestinal glucuronidation and is also shown to increase the bioavailability of curcumin (177) from CL. Piperine enhances the antioxidant and anti-inflammatory activities of thymoquinone (178) from NS. Piperine a component of black pepper,acts as an excellent bio-enhancer to improve the bioavailability of drugs with poor ADMET properties (175). Some study also indicates that piperine shows synergistic effects when taken in combination with various classes of drugs. Piperine represents diverse biological activities, such as anti-inflamatory, anticancer, antiviral, antialzheimer's, antidepressant etc.(175). Piperine is an alkaloid responsible for the pungency of black peeper. Piperine is a PPAR-g agonists, a ligand activated transcription factor in adipocytes and macrophages that increase adipocyte differentiation and insulin sensitivity. Therefore piperine is a potential antidiabetic agent (176). Resulting *P. Nigrum* when added, its bioactive component of piperine ameliorates the efficacy of herbal formulations in accordance with CBTT model in antioxidental-/antidiabetic-/anti-inflammatory- and bioavailability concern.

All the symptomatic patients I treated with CBTT model along with paracetamol (to control fever), azithromycin (to control secondary infections) and antiallergic medications (like tablet manufactured by branded company) of which composition was montelukast (MLK) sodium 10mg and levocetirizine (LCZ) hydrochloride 5mg. Montelukast sodium, an anti-asthmatic/antileukotriene/anti-inflammatory drug sinergistically may have some role to control COVID-19, need to explore and recently reported by Yongkang Chen *et al.*, 2020, that it can irreversibly inhibit the infectivity of Zika like flavivirus (181) and dengue like flavivirus (182). Levocetirizine may stop cytokine storm as it inhibits the production of intercellular adhesion molecule-1 (ICAM-1) and secretion of interleukin IL-6 and IL-8, which may have beneficial effects on the pathophysiologic changes related to human rhinovirus (HRV) infection (183). Without the said AAMs, delaying the recovery by 7 days, I observed. Present results suggest that both montelukast sodium and levocetirizine hydrochloride, the two bitter (184) chloro compounds (185,186), may be repurposed against SARS-CoV-2 either combinedly or alone (191) need to explore in an isolated further study. In case of moderate symptom, mild respiratory distress/feeling of unwell due to silent hypoxia were managed successfully by administering decoction of boiled anti-inflamatory Indian traditional herb, *Abroma augusta* Linn. (Indian Ulatkambal) leaves (collected from Institute garden), extracted with 50% ethanol administering orally. In case of suspected severe symptomatic, respiratory distress were controlled with the hydroalcoholic (50%) leaf-extract of the same herb *A. augusta* of which anti-inflammatory and/anti-asthmatic activity was increased by adding *Osimum sanctum* leaves, *Zingiber officinale*, black tea and *Piper nigrum*. The PHF was thus called AALHAEplus. In no cases, oxygen and/inhaler/nebuliser were required. *A. augusta* leaves are enriched with high level of quercetin, ascorbic acid and gallate equivalents like strong anti-

oxidants, anti-inflammatory, antiproliferative, antimutagenic and anticancer (187) and important elements like cobalt, nickel, iron, calcium and magnesium (188,189). Apart from this I can say I have long experience on AALHAE hebal formulation, which I implimented on more than 100 old asthma patients, more than 90% of which were get rid of this ailments permanently, except few COPD asthma (data preserved for patent filing).

CONCLUSION

The efficay of hypothetical CBTT model thus constructed by reviewing a long database on the therapeutic properties of SITBP/S from several search engines and wider internets has been proved partially from its implimentation study on a very small group of COVID-19 suspected symptomatic patients who were denied to go hospital. Mild and moderate symptomatic patients when treated with CBTT model + AZ in absence of AAMs, delay of recovery by 7 days in each case were observed. Therefore, the treatment model, CBTT which I proposed thus found to be effective with AZ in presence or absence of AAMs which further suggesting that no dought, the model CBTT+AZ+AAMs may be repurposed for faster recovey. Therefore it is rational to say that CBTT treatment acted in this study as an anti-COVID-19 eqivalent likely to be a natural alternative of CQ/HCQ as antiviral concern. In severe symptomatic patients I could not take any risk of without AAMs, both they were treated with AAMs (1 tablet/day for 4 weeks) along with other specific medications said before. For full proof need more systematic further study. Any of the formulation either aqeous/boiled decoction may be effective, as from traditional point of view. But in this study, boiled decoction followed by hydro-alcoholic extract (50%) of herbs followed by filtration through double cheese cloth, thus the filtrate fractions obtained were found to be effective. Ethanol was used as alcohol to prepare ISHAE in this study. The CBTT model consists of 6 point herbal approach. If any body has any allergy-history of any point or any allergic reaction against said di-/tri-/polyherbal formulation, should stop immediate and need consult a physician. In my Herbal Clinic of Chichuria Institute of Medical Science and Researh (registered under government of West Bengal), have more than 10 years of experience on polyherbal formulation of traditional plants/spices, resulting I have applied said Diherbal formulation as preventive to a whatsap group of my friends, more than 20 persons of 35-65 years of age range, advices were served over the telephone to maintain social distance since last 2 months during lockdown. No body heard to get symptomatic. Apart from that also mild, moderate and severe COVID-19 suspected symptomatic patients were treated with PHF successfully following the CBTT model along with combination of paracetamol and/azithromycin and/antiallergic medications and/occasionally by cough syrup. Their family members 15-70 years of age range, were treated for prophylactic treatment with triherbal formulation (THF). None of them appeared symtomatic even after 2 months. No body was neither medicated during the course of herbal treatment nor self-medicated with CQ/HCQ. All the said herbal formulations of bitter plants/spices could be considered as a part of Indian Traditional medicines (ITM) and can be prescribed along with standardised specific allopathic medications as a need based treatment. Finally, It is rational to say that the CBTT model might be a preventive/prophylactic and or alternative least side effective treatment unlike CQ/HCQ therapy of immense side effects, against novel corona virus (nCoV) but prior to that need to arrange *in vitro* preclinical and *in vivo* proper clinical trials.

As the elements of CBTT model are cheap, easily available ingradients, poor, even the Indian adivasi/tribal people of remote/village area, can easilly access the leaves/seeds/rhizome, components of SITBP/S and easily can self prepare the aqueous extract (SPAE) by themselves at home/directly crushing and chewing by teeth also and able to self-medicate themselves as accustomed with traditional practice. As The Ayurveda medicinal system employs a holistic approach to health utilising the synergistic properties of organic resources, SITBP/S require greater scientific validation for their use, though synergistic multi-herbal formulation significantly greater input within the realm of alternative treatment. At the end I can say, herbal/non-pharmacogical treatment (if it acts) is better rather than pharmacological treatment of adverse side effects.

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BIOGRAPHY

Dr. Dipankar Bhattacharyya has more than 28 yrs of research and teaching experience. He has worked in several University and Institutes. He has more than a dozon of National & International Res. Publications, including patents and review.

Journey of life he started from Purba Chichuria Primary School to JCM High School Topper(1982) at 10th level exam. & 12th level studied at the same school. Then Chem.(Hons.) from Ranaghat College(CU) & Biochem.(M.Sc.) from Ballygung Sc. College(CU).

Position and Places where he served are shown below:

1. Former JRF, Dept. of Physics, JU, Kolkata
2. Former Ph.D. scholar and Res. Associate, Dept. of Chem., Bose Institute+JU, Kolkata
3. Former Post Doc Fellow, Cent. for Mol. Neurobiology, The OSU, USA
4. Former Lecturer(Cont.), Dept. of Microbiol., BKG College(CU), Howrah
5. Former Sr. Asst. Professor, PG Dept. of Biochem., OIST, VU
6. Present position & address: Principal Investigator, Chichuria Institute of Medical Science & Research, Vill+PO-Chichuria, Nadia, WB-741126, where he developed & discovered lot of medicines:

•Asthma Mukti Prakitik as antiasthma,
•Gas-ambal Mukti Prakitik as antiulcer,
•Baytha Mukti Prakitik Message oil as pain reliever and
•several other natural medicines also.

In addition to that he also wrote an "Easiest way to memorize the Long Form of Periodic Table" (অদীপসা) in Chemistry.

Recently he hypothesised:
"Reposition of Montelukast either alone or in combination with levocetirizine against SARS-CoV-2", published in Med Hypothesis, 144, 2020, 110046.

His hypothesis of COVID-19 medicines were also accepted by World Health Organisation (WHO). ID: covidwho-627612.

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