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Original Research Article

Immunomodulatory Effect of Various Herbs Used in *Murchana* (Refining) of *Ghrita Kalpana* (An Ayurvedic Oleaginous Medicament)

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Abstract

Introduction: Ayurvedic dosage forms hold a unique place in pharmaceutics and therapeutics. *Sneha Kalpana* is a group of products of medicated *taila* and *ghee*. *Murchana* is the first step towards any *Sneha paka* process. It is a special pharmaceutical procedure before subjecting the drugs to *Sneha Paka*. For the Preliminary treatment of *ghrita* (Refining of *ghrita*) six herbal drugs are added to it. These herbal drugs are: *Haritki* (*Terminalia chebula*), *Amalaki* (*Emblica officinalis*), *Vibhitaki* (*Terminalia bellirica*), *Mustaka* (*Cyperus rotundus*), *Haridra* (*Curcuma longa*), *Matulunga* (*Citrus medica*). Main aim of *Sneha Murchana* is to remove - *Durgandha* (Bad odor), *Amadhosha* (Unrefined ghee), *Ugrata* (Sharpness). *Ghrita* (Cow's ghee) is a potent ingredient capable of promoting memory, intellect, power of digestion, semen levels and *Ojas (ojas* is an essence present in every *dhatu* (tissue) and is responsible for the strength, vitality and immunity of the body.) Various studies have proved immunostimulant activity of Cow's ghee. It can be a possibility that this preliminary refining *Murchana* process of *ghrita* might increase the immunostimulant potential of ghee. This review article focusses on the immunomodulatory potential of the herbs added during *Murchana* process. ***Material and Method:*** Literature related to six *Murchana* herbs have been referred from various ayurvedic texts, modern medical books, research papers and journals. Phytoconstituents of *Murchana dravyas* and anti-oxidant, anti-inflammatory and immunomodulatory effect of *Murchana dravyas* have been compiled from various sources. ***Result and Discussion*:** Various studies have proven anti-oxidant, anti-inflammatory, anti-carcinogenic, immunomodulatory effect of these six *Murchana* herbs. Hence it can be concluded that along with other benefits refining '*Murchana'* process of *ghrita* might increase the immunostimulant potential of ghee.

Keywords: *Murchana, Sneha Kalpana,* Anti-oxidant, Anti-inflammatory immunomodulation, Anti-carcinogenic.

INTRODUCTION

Ayurvedic dosage forms hold a unique place in pharmaceutics and therapeutics. *Sneha Kalpana* is a group of products of medicated *taila* and *ghee*. These drugs are treating very wide range of diseases among patients of all age groups. *Sneha Kalpana* may be defined as "A pharmaceutical process to prepare oleaginous medicaments from the substances like *Kalka* (herbal paste of different parts of botanicals), *Kwatha* (specifically prepared decoction in accordance of Ayurvedic principles) or *Drava dravya* (any other liquid such as milk, self expressed juices, meat juice, etc.) taken in specific proportion and by subjecting them to unique heating pattern and duration to fulfill certain pharmaceutical parameters, according to the need of therapeutics." Aim of this arrangement is mass transfer of the lipid-soluble active principles of all treated herbal drugs and material of animal and mineral origin into the oleaginous medium. *Murchana* is the first step towards any *Sneha paka* process. It is a special pharmaceutical procedure before subjecting the drugs to *Sneha paka*. For the Preliminary treatment of *ghrita* (refining of *ghrita*) six herbal drugs are added to it. These herbal drugs are: *Haritki* (*Terminalia chebula*), *Amalaki* (*Emblica officinalis*), *Vibhitaki* (*Terminalia bellirica*), *Mustaka* (*Cyperus rotundus*), *Haridra* (*Curcuma longa*),

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Matulunga (*Citrus medica*) [[i]]. This preliminary treatment of ghee is called as '*Sneha Murchana*'. Main aim of *Sneha Murchana* is to remove - *Durgandha* (Bad odor), *Amadhosha* (Unrefined ghee), *Ugrata* (Sharpness). After *Sneha Murchana*, *Sneha* will acquire the following qualities such as : good smell and colour, potency of *sneha* gets enhanced so that it can imbibe more active principles from the drug with which it is processed, *sneha* takes up the active principles present in the *Murchana dravyas*, it increases the solubility , absorption and potency of the finished product, it is capable of *Amadoshaharatwa* which is the removal of '*Ama'* which can be correlated to the 'moisture content' which can be directly related to rancidity problems. *Acharya Charaka* has described *ghrita* as a potent ingredient capable of promoting memory, intellect, power of digestion, semen levels and *Ojas (ojas* is an essence present in every *dhatu* (tissue) and is responsible for the strength, vitality and immunity of the body.) Various studies have proved immunostimulant activity of Cow's ghee. This preliminary refining *Murchana* process of *ghrita* might increase the immunostimulant potential of ghee. This review article focusses on the immunomodulatory potential of the herbs added during *Murchana* process.

MATERIAL AND METHOD

Source of data

Literature related to six *Murchana* herbs have been referred from various ayurvedic texts, modern medical books, research papers and journals.

METHODS

- To compile ayurvedic properties and action of *Murchana dravyas.*
- To compile the phytoconstituents of *Murchana dravyas.*
- To emphasize the immunomodulatory effect of *Murchana dravyas.*

DRUG REVIEW

Table 1: ***Ayurvedic Properties & action of Murchana Dravyas* of *Ghrita***

S. No	DRUGS	BOTANICAL NAME	RASA	GUNA	VIRYA	VIPAKA	KARMA (Acc. To API)
1.	*Haritaki* [ii]	*Terminalia chebula* Retz.	*Kashaya, Pancharasa*	*Laghu, Ruksha*	*Ushna*	*Madhur*	*Chakshushya, Rasayana, Medya, Hrydya, dipan,Sarvadoshaprasaman*
2.	*Vibhitaki* [iii]	*Terminalia bellirica* Roxb.	*Kashaya*	*Laghu, Ruksha*	*Ushna*	*Madhur*	*Chakshushya,Keshya,Kriminasana,Kasahara ,Kaphpittajit*
3.	*Amalaki* [iv]	*Emblica officinalis* Gaertn.	*Amlapradhan Panchrasa*	*Laghu, Ruksha*	*Sheeta*	*Madhur*	*Rasayana,Tridosajit,Vrsya,Chakshushya*
4.	*Haridra* [v]	*Curcuma longa* Linn.	*Tikta, Katu*	*Laghu, Ruksha*	*Ushna*	*Katu*	*Krimighna,kaphapittanut,varnya,vishghna*
5.	*Mustaka* [vi]	*Cyperus rotundus* Linn.	*Tikta, Katu, Kashya*	*Laghu, Ruksha*	*Sheeta*	*Katu*	*Pittkaphahara,Sothahara,pachana,Jvaraghna*
6.	*Matulunga* [vii]	*Citrus medica* Linn.	*Amla*	*Laghu, Snighdha*	*Ushna*	*Amla*	*Tridoshhar,Dipan,Pachan*

Table no.2 : Part used and quantity of herbs used in *Murchana* of 1*prastha* (768gm) *go ghrita*[i]

S. No	DRUGS	PART USED	QUANTITY
1.	*Haritaki*	Pericarp	1 *pala* (48 gms)
2.	*Vibhitaki*	Pericarp	1 *pala*
3.	*Amalaki*	Pericarp	1 *pala*
4.	*Haridra*	Rhizome	1 *pala*
5.	*Mustaka*	Rhizome	1 *pala*
6.	*Matulunga*	Fruit juice	1 *pala*

PHYTOCONSTITUENTS OF VARIOUS HERBS USED IN SNEHA MURCHANA–

1. *Haritki* (*Terminalia chebula*) [viii]

Terminalia chebula fruit is rich in tannic acid.

The chief constituents of tannic acid are chebulic acid, chebulagic acid, corilagin and gallic acid.

Tannic acid of *Terminalia chebula* is of pyrogallol (hydrolyzable) type.

There are 14 components of hydrolysable tannins -gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-H-D-glucose, 1,6-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin.

Terminalia chebula is having 32% tannic acid content which varies with the geographical variation.

Terminalia chebula also contains terflavin B, a type of tannin.

Fructose, Amino acids, succinic acid, β sitosterol, resin and purgative principle of anthroquinone and sennoside are also present.

Flavonol glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin as well as other phenolic compounds like 2,4-chebulyl-β-D-glucopyranose, ethyl gallate, punicalagin, terflavin A, terchebin, luteolin are also present.

Triterpenes Glycosides-arjunglucoside I, arjungenin, and the chebulosides I and II.

2. *Vibhitaki* (*Terminalia bellirica*) [ix]

Flavone- 7-hydroxy 3', 4'(methylenedioxy) flavone, luteoline

Steroids -β- sitosterol

Lignans- Termilignan, thannilignin, anolignan B

Tannins- Gallic acid, ellagic acid, methyl gallate, ethyl gallate (Phenyllemblin), chebulagininc acid, chebulagic acid, hexahydroxydiphenic acid ester Glycosides Fructose, sucrose, galactose, D-glucose, mannose, rhamnose.

Terpenoid- Belleric acid, chebulagic acid, arjungenin

Saponin- Bellericoside and bellericanin

Cardenolide- Cannogenol 3-O-β-galactopyranosyl-(1→4)-Oα-L-rhamopyranoside

Flavonol aglycones -Quercetine and kampferol

Flavonol glycosides- Quercetin-3-O-[6''-α-L-rhamnopyranosyl]- (1→6)-β-D-glucopyranoside (rutin), quercetin3-O-α-L-rhamnopyranoside, quercetin-3-O-βD-glucopyranoside and kaempferol-3-O-β-Dglucopyranoside

Fatty acids present in oil -Palmitic acid, linoleic acid, stearic acid, myristic acid and oleic acid

Glycerides of fatty acids- Palmitooleolinolein, stearo-oleolinolein, palmitodiolein, stearodiolein, dioleolinolein and triolein.

3. *Amalaki* (*Emblica officinalis*) [x]

Ascorbic acid (vitamin C) - most abundant constituent.

Fatty acids - linolenic, linoleic, oleic, stearic, palmitic and myristic acids.

Sugars -D-glucose, D-fructose, D-myo-inositol, D-galacturonic acid, D-arabinosyI, D-rhamnosyl, D-xylosyI, D-glucosyI, D-mannosyl and D-galactosyI

Tannins -Emblicanin A (37%) and Emblicanin B (33%), pedunculagin (14%) and punigluconin (12%)

Other compounds isolated from this plant-Gallic acids, amlaic acid, arginine, aspartic acid, astragallin, β-carotene, β-sitosterol, chebulagic acid, chebulic acid, chebulaginic acid, chebulinic acid, corilagic acid, corilagin, cysteine, ellagic acid, emblicol, gibberellins, glutamic acid, glycine, histidine, isoleucine, kaempferol, leucodelphinidin, methionine, phenylalanine, phyllantidine, phyllemblic acid, quercetin, riboflavin, rutin, thiamin, threonine, tryptophan, tyrosine, valine, zeatin, fixed oils, phosphatides, essential oils, minerals, vitamins, aminoacids etc.

4.*Mustaka* (*Cyperus rotundus*) [xi]

Different phytochemical studies on *C.rotundus* revealed the presence of :- Alkaloids, flavonoids, tannins, starch, glycosides, furochromones, monoterpenes, sesquiterpenes, sitosterol, fatty oil containing a neutral waxy substance, glycerol, linolenic, myristic and stearic acids.

The major compounds isolated from essential oil and the extracts of *C.rotundus* rhizome are :-Alpha-cyperone, Alpha-rotunol, Beta-cyperone, Beta-pinene, Beta-rotunol, Beta-selinene, Calcium, Camphene, Copaene, Cyperene, Cyperenone, Cyperol, Cyperolone Cyperotundone D-copadiene, D-epoxyguaiene, D-fructose, D-glucose, Flavonoids, Gamma-cymene, Isocyperol, Isokobusone, Kobusone, Limonene, Linoleic-acid, Linolenic-acid, Magnesium, Manganese,

C. rotunduskone, Myristic-acid, Oleanolic-acid, Oleanolic-acid-3-o-neohesperidoside, Oleic-acid, P-cymol, Patchoulenone, Pectin, Polyphenols, Rotundene, Rotundenol, Rotundone, Selinatriene, Sitosterol, Stearic-acid, Sugeonol, Sugetriol.

C.rotundus contains an essential oil that provides for the characteristic odour and taste of the herb, comprised mostly sesquiterpene hydrocarbons, epoxides, ketones, monoterpenes and aliphatic alcohols.

Sesquiterpenes include:- Selinene, isocurcumenol, nootkatone, aristolone, isorotundene, cypera-2,4(15)-diene, and norrotundene, as well as the sesquiterpene alkaloids rotundines A-C.

Other constituents:- Ketone cyperadione, and the monoterpenes cineole, camphene and limonene.

C.rotundus has also been shown to contain miscellaneous triterpenes including oleanolic acid and sitosterol, as well as flavonoids, sugars and minerals.

The chemical composition of the volatile oils of *C.rotundus* has been extensively studied and four chemotypes (H-, K-, M- O-types), of the essential oils from different parts of Asia have been reported.

5.*Haridra* (*Curcuma longa*) [xii]

The major constituents- curcumin (60%), Curcumin desmethoxycurcumin, mono demethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin and cyclocurcumin.

By the oxidation of curcumins vanillin can be yielded.

Curcumin (diferuloylmethane) (3-4%) is responsible for yellow color and comprises of curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Demethoxy and bis-demethoxy derivatives of curcumin have also been isolated.

Essential oil (5.8%) obtained by steam distillation of rhizomes has - phelladrene (1%), sabinene (0.6%), Cineol (1%), borneol (0.5%), Zingiberene (25%) and sesquiterpines (53%).

6.*Matulunga* (*Citrus medica*) [xiii]

It contains good amount of citric acid, glucose and sulphuric acid.

Peel contains volatile oil containing citrine (76%), citrol (7-8%), cymene and citronellal.

Other constituents in the leaves and peels oil - Linalool, γ-terpinene, (Z)-citral, (E)-citral, citronellal, citronellol, citronellyl acetate, isopulegol, r-cymene, geranial, citronellic acid, α-terineol.

Erucylamide and isolimonene are the most important and main components in leaf and peel oil.

The constituents of *Citrus medica* var. sarcodactylis have been isolated and purified. Nine compounds were isolated and identified as 5-methoxyfurfural, 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one, diosmetin, diosmin, obacunone, aviprin, 3-(3-methoxy-4-hydroxyphenyl)-acrylic acid, vanillic acid and 3,4-dihydroxy-benzoic acid.

Immunomodulatory effect of herbs used in *Sneha Murchana*:-

1. *Haritki* (*Terminalia chebula*)

1. Immunomodulatory Activity

1. In a study done to investigate immunomodulatory effect of alcohol extract of *Terminalia chebula* Retz combretaceae dried ripe fruits at cellular level it was found out that *Terminalia chebula* extract (100 mg/kg/p.o.) increased the level of liver mitochondrial enzymes (CAT and SO) as well as GSH but decreased the level of LPO in the liver when compared to the vehicle, sheep red blood cells (SRBC) and cyclophosphamide-treated groups. Secretion of melatonin by pineal gland was enhanced by *T. chebula* treatment. The extract also increased spleen lymphocyte proliferation. Based on RT-PCR analysis, the expression of cytokines, viz, IL-2, IL-10 and TNF-α was more in *T. chebula*-treated than in vehicle- and cyclophosphamide- treated groups [xiv].
2. The study on aqueous extract of *T. chebula* for its immunomodulatory activity based on assessment of humoral antibody titre and delayed type hypersensitivity (DTH) test has been reported [xv].
3. A detailed study on immunomodulatory activity of its aqueous extract has also been reported, where the model animals were pretreated with 500 mg/kg of extract orally and challenged with 50 000 CFU of *S. typhimurium*. The animals showed 3×103/mm3 increase in WBC count and 4% increase in lymphocyte count as compared to saline treated control animals. It was also reported that there was 102% increase in lymphocyte proliferation and 28.87% increase in foot pad thickness as compared to the infected control in DTH test. Thus the study concluded that the extract shows its protective effect through its immunomodulatory activity in mice against typhoid [xvi].
4. The biologically active compounds such as chebulagic acid, gallic acid and ellagic acid make *T. chebula* highly potent antioxidant, which may be responsible for its immunomodulatory activity [xvii, xviii, xix].
5. The extract of *T. chebula* neutralizes reactive oxygen species (ROS) and scavenges free radicals. The free radicals are responsible for

causing inflammation by stimulating release of cytokines such as IL-1, TNF-α and IFN-β, which stimulate additional neutrophils and macrophages at site of inflammation [xx]. Thus, different antioxidants of the extract exhibit immunosuppressive properties, which help in neutralizing these important inflammatory mediators.

6. One of the study described that *T. chebula* alcoholic extract shows immunomodulatory activity. The various parameters determined were differential leukocyte count (DLC), phagocytic activity and zinc sulphate turbidity (ZST) test. Oral administration of *T. chebula* alcoholic extract (100 mg/kg) was found to increase the neutrophils and lymphocytes as compared to vehicle and cyclophosphamide treated groups. *T. chebula* alcoholic extract showed linear time dependent significant phagocytic activity as compared to SRBC sensitized and cyclophosphamide treated group. In zinc sulphate turbidity test *T. chebula* treated rats serum showed more turbidity (cloudy) which indicate the increase in the immunoglobulin level as compared to vehicle, SRBC sensitized and cyclophosphamide treated group. So it is revealed that the alcoholic extracts of *T. chebula* obtained from the dried ripe fruits possess good immunomodulatory activity [xxi].

2. Anti-oxidant Activity

1. A study was done to determine the difference of antioxidant activities between unfermented extracts and fermented products for *Terminalia chebula* Retzius, and to recognize antioxidative patterns. The methanol extract, water extract, 95% ethanol extract, fermented product of dried powder at 25 °C and fermented product of residues after 95% ethanol extraction at 37 °C showed good antioxidant activities based on the scavenging effect of 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) assay and the horseradish peroxidase (HRP)-luminol-hydrogen peroxide (H2O2) assay, respectively. The methanol extract, water extract, 95% ethanol extract, fermented product of dried powder at 15 °C and fermented product of water extract at 25 °C exhibited a good value of antioxidant activity based on the pyrogallol-luminol assay [xxii].
2. Warm water extract of *Terminalia chebula* was studied for their antioxidant activity. 3 extracts and 4 compounds were investigated for it' anti-lipid peroxidation, anti-superoxide radical formation and free radical scavenging activities. The results showed that the all tested extracts of *Terminalia chebula* exhibited antioxidant activity at different magnitude of potency [xxiii].
3. In a study to compare the antioxidant efficacy and the phenolic content of two hexane extracts viz. 'Hex 1' and 'Hex 2' of fruits of *Terminalia chebula* prepared by maceration and sequential method, respectively. The extracts were tested for their relative levels of antioxidant activity and the total phenolic content using DPPH, deoxyribose, reducing power, chelating power, lipid peroxidation and Folin-Ciocalteu method. From the results, it was concluded that phenolic compounds were predominant in the 'Hex 2' prepared by sequential extraction method. The antioxidative potential of 'Hex 2' was also far superior to the 'Hex 1' prepared by maceration method [xxiv].
4. Methanolic extracts of *T. chebula* fruit was studied. The *T. chebula* fruit meat extracts showed highest total phenolic content and antioxidant activity. The study indicated that the antioxidant activity was directly proportional to the amount of total Phenols [xxv].
5. Antioxidant role of *Terminalia chebula* aqueous extract was evaluated against age-related oxidative stress in heart tissues of young and aged rats. The result showed that *T. chebula* aqueous extract modulates the activities of antioxidants and lipid peroxidation through the management of oxidant/antioxidant imbalance in rat heart tissues [xxvi].
6. *In-vitro* antioxidant activity of Petrol, Ether, benzene, chloroform, ethyl Acetate, 70% ethanol and water extract was found to be having high antioxidant activity and radical scavenging activity against various antioxidant systems in vitro [xxvii].
7. Aqueous extracts of Different medicinal plants, *viz*., *Momardica charantia* Linn (e1), *Glycyrrhiza glabra* (e2), *Acacia catechu* (e3), *Terminalia bellirica* (e4), *terminalia chebula* (e5) And *Emblica officinalis* (e6), and combination drug, *Triphala* (e7), containing equal amounts of e4, e5 and e6, has been evaluated for the antioxidant activity. e1 and e2 did not show any antioxidant activity and have very low ascorbate Equivalents. e3 acts as a moderate antioxidant, while e4, e5, e6 and e7 are very good antioxidants and are rich in phytochemicals which have high antiradical activity properties [xxviii].
8. Researchers concluded from the study of the 70% methanol extract of the fruits of *Terminalia chebula*, *Terminalia bellirica* and *Emblica officinalis*, the fact that they might be useful as potent Sources of natural antioxidant [xxix].
9. Antioxidant activity of ethanolic extract of fruits of *Terminalia chebula* (500 mg/kg body wt, orally for 30 days) against Isoproterenol-induced oxidative stress was investigated in rats [xxx].

10. Oral administration of ethanol extract of *Terminalia chebula* Fruit at a concentration of 200 mg/kg body weight for 30 days significantly controlled the alteration in the levels of thiobarbituric acid reactive substances, hydroperoxides, and both enzymatic and nonenzymatic antioxidants [xxxi].

3. Anti-Cytotoxic Activity

Gallic acid and chebulagic acid were isolated from the extract of a herbal medicine, *Kashi* (myrobalans: the fruit of *Terminalia chebula*) as active principles that blocked the cytotoxic tlymphocyte (ctl)-mediated cytotoxicity [xxxii].

2. *Vibhitaki* (*Terminalia bellirica*)

1. Immunomodulatory Activity

1. Immunomodulatory activity of ethanolic extract of *T. bellirica* (150 and 350 mg/kg, p.o.) was carried out by testing delayed type hypersensitivity (DTH) reaction, phagocytic index, cyclophosphamide induced neutropenia and relative organ weight. Pretreatment with both the doses of ethanolic extract of *T. bellirica* significantly ($p<0.01$) potentiated the DTH reaction by facilitating the footpad thickness response to SRBC's in sensitized mice. Moreover, pretreatment with ethanolic extract of *T. bellirica* (350 mg/kg, p.o.) showed significant ($p<0.01$) increase in phagocytic index and significant ($p<0.05$) protection against cyclophosphamide induced neutropenia. Furthermore, significant ($p<0.01$) increase in relative weight of spleen at 350mg/kg was observed but there was no remarkable change in thymus index observed in tested doses of plant extract. So, the study demonstrated that *T. bellirica* triggers both non-specific and specific cellular immunity [xxxiii].
2. The immunomodulatory activity of an acetone extract of *T. bellirica* fruit was studied by Mitogen induced-lymphocyte proliferation using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) technique, Th1-andTh2-related cytokine production by lymphocytes using ELISA and peritoneal macrophage function in ICR mice were assayed. The results showed that the extract had a mild inhibitory effect on the generation of oxidase enzyme (Phagocytic Index 0.8, 100 μg/ml) but did not influence acid phosphatase enzyme function during phagocytosis. The extract stimulated the proliferation of both T and B lymphocytes. The maximal activation (Stimulation Index 3.2, 100 μg/ml) was presented with concanavalin A induction, indicating a major effect on T lymphocyte proliferation. The extract reduced the production of IFN-γ (89%, 100 μg/ml) and IL-2 (98%, 100 μg/ml) but increased IL-10 secretion (231%, 100 μg/ml) compared to concanavalin A. Gallic acid, a pharmacological component contained in this plant, presented a similar effect as that of *T. bellirica* extract and may contribute to the immunomodulatory activity of *T. bellirica* fruits in cooperation with other phytocompounds [xxxiv].

3. *Amalaki* (*Emblica officinalis*)

1. Antioxidant activity

1. Ethyl acetate extract of Amla has been reported to reduce the elevated levels of urea nitrogen and serum creatinine in aged rats. Oral administration of this extract significantly reduced the thiobarbituric acid-reactive substance levels of serum, renal homogenate and mitochondria in aged rats, suggesting that amla would ameliorate the oxidative stress under aging. Increased inducible nitric oxide synthase and cyclooxygenase (COX)-2 expression in the aorta of aging rats were also significantly suppressed by ethyl acetate extract of amla. This extract reduced the COX-2 and nitric oxide synthase expression levels by inhibiting NF-kappa B activation in the aged rats. Thus, Amla would be a very useful antioxidant for the prevention of age-related renal disease [xxxv].
2. Pre-feeding of Amla appeared to reduce the hexachlorocyclohexane (HCH)-induced raise in renal gamma-glutamyl transpeptidase (GGT) activity. This shows the elevation of hepatic antioxidant system and lowering of cytotoxic products as which were otherwise affected by the administration of HCH [xxxvi].
3. Rats were examined for the antioxidant properties of Amla extracts and its effect on the oxidative stress in streptozotocin induced diabetes was also reported. The extracts showed strong free radical scavenging activity. Amla extracts orally administered to the diabetic rats slightly improved body weight gain and also significantly increased various oxidative stress indices of the serum of the diabetic rats. Moreover the decreased levels of albumin in the diabetic rats were significantly improved with this drug. It also significantly improved the serum adiponectin levels. Thus, amla can be used for relieving the oxidative stress and improving glucose metabolism in diabetes [xxxvii].
4. *E. officinalis* is used to protect the skin from the devastating effects of free radicals, non-radicals and transition metal induced oxidative stress. It is suitable for use in antiaging, general purpose skin care products and as sunscreen [xxxviii].
5. *E. officinalis* fruits contain tannoid principles that have been reported to exhibit antioxidant activity *in vitro* and *in vivo*. Emblicanin-A (37%) and -B (33%) enriched fractions of fresh

juice of *E. officinalis* fruits were investigated for antioxidant activity against ischemia-reperfusion-induced oxidative stress in rat heart. The study confirmed the antioxidant effect of *E.officinalis* and also indicated that the fruits of plant may exhibit a cardioprotective effect [xxxix].

6. The antioxidant activity of *E. officinalis* extract associated with the presence of hydrolyzable tannins having ascorbic acid like action have been also reported [xl].
7. *E. officinalis* contains tannoid principles comprising of emblicanin A, emblicanin B, punigluconin and pedunculagin, which have been reported to posses antioxidant activity *in vitro* and *in vivo* [xli].
8. Ellagic acid, as a powerful antioxidant present in *E. officinalis*, has the ability to inhibit mutations in genes and repairs the chromosomal abnormalities [xlii].
9. *E.officinalis* has been reported to inhibit chromium induced free radical production, and it restored the antioxidant status back to control level. It also inhibited the apoptosis and DNA fragmentation induced by chromium. It relieved the immunosuppressive effect of chromium on lymphocyte proliferation, and even restored the IL-2 and gamma-IFN production [xliii].
10. The cytoprotective and immunomodulating properties of *E.officinalis* against chromium (VI) induced oxidative damage have been reported. These workers observed that the chromium (VI) at 1 µg/ml was highly cytotoxic; it enhanced the free radical production and decreased the reduced glutathione (GSH) levels and glutathione peroxidase (GPx) activity in macrophages. However, the presence of Amla resulted in an enhanced cell survival, decreased free radical production and higher antioxidant levels similar to that of control cells. Further, chromium (VI) treatment resulted in decreased phagocytosis and gamma-interferon production, while amla inhibited the chromium induced immunosuppression and restored both phagocytosis and gamma-interferon production by macrophages significantly [xliv].
11. Immunomodulatory role of *Emblica officinalis* in arsenic induced oxidative damage and apoptosis in thymocytes of mice was studied. It was found out that Arsenic exposure to mice caused a significant increase in the lipid peroxidation, ROS production and decreased cell viability, levels of reduced glutathione, the activity of superoxide dismutase, catalase, cytochrome c oxidase and mitochondrial membrane potential in the thymus as compared to controls. Increased activity of caspase-3 linked with apoptosis assessed by the cell cycle analysis and annexin V/PI binding was also observed in mice exposed to arsenic as compared to controls. Co-treatment with arsenic and Amla decreased the levels of lipid peroxidation, ROS production, activity of caspase-3, apoptosis and increased cell viability, levels of antioxidant enzymes, cytochrome c oxidase and mitochondrial membrane potential as compared to mice treated with arsenic alone. The results of the present study exhibited that arsenic induced oxidative stress and apoptosis was significantly protected by co-treatment with amla that could be due to its strong antioxidant potential [xlv].

2. Immunomodulatory Activity

1. *E.officinalis* and *Evolvulus alsinoides* (*Shankhpushpi*) were assessed for immunomodulatory activity in adjuvant induced arthritic (AIA) rat model. Complete Freund's Adjuvant (CFA) was injected in right hind paw of the animals induced inflammation. Lymphocyte proliferation activity and histopathological severity of synovial hyperplasia were used to study the anti-inflammatory response of both the extracts, which showed a marked reduction in inflammation and oedema, and caused immunosuppression in AIA rats, indicating that these drugs may provide an alternative approach for the treatment of arthritis [xlvi].
2. The immunomodulatory activity of the combined extracts of *O. sanctum, W. somnifera* and *E. officinalis* was noticed [xlvii].
3. *E. officinalis* fruit administered orally at different concentrations (100, 250, 500 mg/kg) for 7consecutive days in Swiss albino mice prior to a single intraperitoneal injection of DMBA, decreased the frequency of bone marrow micronuclei. The protection provided by *E. officinalis* fruit may be due to its antioxidant capacity and through its immunomodulatory effect on hepatic activation and detoxifying enzymes [xlviii].
4. Cyclophosphamide is one of the most famous alkylating anticancer drugs in spite of its toxic side effects, including hematotoxicity, immunotoxicity and mutagenicity. *E. officinalis* may be the beneficial as a component of combination therapy in cancer patients under cyclophosphamide treatment [xlix].
5. Two samples of *Āmalaki Rasāyana* (AR7 and AR21) were studied to evaluate comparative immunomodulatory activity against the cyclophosphamide immunosuppression in rats.
6. It was found that *Āmalaki Rasāyana* possesses significant immunostimulant activity and moderate cytoprotective activity.AR21 was found to have better activity profile in terms of both immunostimulant as well as cytoprotective activity [l].

7. Aqueous extract of dried *Emblica officinalis* Gaertn. (Amla) fruit pulp powder was evaluated for immunomodulatory effect on male Swiss Albino mice. The mice were divided into three groups. The first group received vehicle alone to serve as control. The second and third groups received the extract orally at 100 and 200 mg/ kg body weight dose levels respectively per day for a period of 19 days. There was significant dose dependent increase in haemagglutination antibody titre, sheep red blood cells induced delayed type of hypersensitivity reaction, macrophage migration index, respiratory burst activity of the peritoneal macrophages, total leukocyte count, percentage lymphocyte distribution, serum globulin and relative lymphoid organ weight in *Emblica* treated mice indicating its ability to stimulate humoral as well as cell mediated immunity along with macrophage phagocyte [li].
8. The effect of *Emblica officinalis* (EO) derived tannins on humoral immune responses and their protective efficacy against *Eimeria* infection in chickens was studied. Tannins were extracted from EO and characterized by HPLC. EO derived tannins (EOT) and commercial tannins (CT) were orally administered in broiler chicks in graded doses for three consecutive days, that is, 5th-7th days of age. On day 14 after administration of tannins, humoral immune response was detected against sheep red blood cells (SRBCs) by haemagglutination assay. Protective efficacy of tannins was measured against coccidial infection, induced by *Eimeria* species. Results revealed higher geomean titers against SRBCs in chickens administered with EOT as compared to those administered with CT and control group. Mean oocysts per gram of droppings were significantly lower ($P < 0.05$) in EOT administered chickens as compared to control group. Lesion scoring also showed the lowest caecal and intestinal lesion score of mild to moderate intensity in chickens administered with EOT. Further, significantly higher ($P < 0.05$) daily body weight gains and antibody titers were detected in EOT administered chickens as compared to those of CT administered and control groups. EOT showed the immunostimulatory properties in broilers and their administration in chickens boost the protective immunity against coccidiosis [lii].

3. Anti-Carcinogenic activity

1. *E. officinalis* inhibits the growth and spread of various cancers, including breast, uterus, pancreas, stomach and liver cancers, and malignant ascites. It reduces the side effects of chemotherapy and radiotherapy [40].
2. *E. officinalis* reduced the cytotoxic effects in mice dosed with carcinogens [liii]. Amla fruit contains 18 compounds that inhibit the growth of tumour cells such as gastric and uterine cancer cells [liv].
3. It enhances natural killer (NK) cell activity in various tumours. Its extract reduced the ascites and solid tumours induced by Dalton's lymphoma ascites cells in mice. The extract also increased the life span of tumour bearing animals [40, lv].
   Emblicanins A and B (tannins) present in *E. officinalis*, have been reported to possess strong antioxidant and anticancer properties [40].
4. Chemoprevention with food phytochemicals is presently considered as one of the most important strategies to control cancer. Chemopreventive potential of amla extract on 7,12-dimethylbenz(a)anthracene (DMBA) induced skin tumorigenesis in Swiss albino mice have been found [lvi].
5. Phenolic compounds derived from amla exhibit a number of beneficial effects and can potentially inhibit several stages of carcinogenesis. Efficacy of the polyphenol fraction of *E. officinalis* on the induction of apoptosis in mouse and human carcinoma cell lines, and its immunomodulatory effect on N-nitrosodiethylamine (NDEA) induced liver tumours in rats was also investigated. The polyphenol fraction of *E. officinalis* could induce the apoptosis in Dalton's lymphoma ascites (DLA) and CeHa cell lines. The polyphenol fraction also inhibited the DNA topoisomerase I in *Saccharomyces cervisiae*, mutant cell cultures and the activity of cdc25 tyrosine phosphatase [lvii].
6. Amla extract was found most active in inhibiting *in vitro* cell proliferation towards human tumour cell lines, including human erythromyeloid K562, T-lymphoid Jurkat, B-lymphoid Raji, erythroleukemic HEL cell lines [lviii].
7. Norsesquiterpenoid glycosides from the roots showed significant antiproliferative activities [45].

4. *Mustaka (Cyperus rotundus)*

1. Anti-Oxidant Activity

1. The in vitro antioxidant activity of the roots and rhizomes of *Cyperus rotundus* L.has been investigated by estimating degree of non-enzymatic haemoglobinglycosylation, measured colorimetrically at 520 nm. The ethanol extract of the rootsand rhizomes of *C. rotundus* showed higher activity, than other extracts of it. The antioxidant activity of the extracts are close and identical in magnitude, andcomparable to that of standard antioxidant compounds used [lix].
2. In a study it was seen that *C. rotundus* extracts contain potent components such as flavonoids that may potentially be useful for modulating the immune cell functions, provoking analgesic, anti-inflammatory and antioxidant effects [lx].

2. Anti-inflammatory Activity

The *Cyperus rotundus* extract (CRE) was examined for its anti-inflammatory properties. This research was focussed on investigating the levels of activated T lymphocytes and the pro-inflammatory cytokines expressed by macrophages. The treatment of CRE reduced the population of CD4 and CD8 T cells. The number of activated CD4 and CD8 T cells were also significantly suppressed. The population of macrophages marked by CD11b cells was significantly reduced. Finally, the CRE treatment suppressed the levels of TNF-α, IFN-γ, IL-1β, and IL-6 expressed by macrophages [lxi].

5. *Haridra* (*Curcuma longa*)

1. Anti- Carcinogenic Activity

In-vivo animal studies examining curcumin's chemosensitizing and radiosensiziting properties have favourably demonstrated the effect of curcumin on Gemcitabine for pancreatic cancer [lxii]. A clinical trial also demonstrated that a curcumin dose of 8 g per day when taken with Gemcitabine is safe and well tolerated as a supplement [lxiii]. Other studies have demonstrated similar effects of curcumin and Docetaxel for ovarian cancer [lxiv], as well as curcumin and oxaliplatin for colon cancer [lxv]. Studies investigating the use of Docetaxel and curcumin as potential treatments for breast cancer have also shown that curcumin can be well tolerated in addition to the chemotherapy [lxvi]. One interesting study of 85 men who underwent prostate biopsies because of elevated prostate specific antigen (PSA) but later had negative biopsies showed that those who took a combination of curcumin and flavonoids for six months had a significantly decreased level of PSA. This study demonstrated that curcumin may play a role in suppressing the production of PSA. Curcumin was also well tolerated in doses up to 12 g per day in patients who were being treated for multiple myeloma. One study demonstrated in 16 chronic smokers, in addition to 6 non-smokers as control, that when given 1.5 g curcumin a day for 30 days, there was a significant reduction in urinary mutagens found, whereas in the control group there was no change in the excretion of mutagens that was observed. Treatment with curcumin in this study was well tolerated, and there were no changes in serum AST, ALT, blood glucose, creatinine or lipid profile observed [lxvii]. This study suggested that not only is curcumin safe, but it could also be used as a dietary modification to decrease the risk of lung cancer.

2. Anti-oxidant activity

Finding based on *in vitro* showed that curcumin is an effective scavenger of ROS and reactive nitrogen species [lxviii, lxix] and in other finding, the antioxidant activity was established by inhibition of controlled initiation of styrene oxidation [lxx]. The effective anticancer property of curcumin is attributed to its antioxidant effect that control DNA damage and free radical–mediated lipid peroxidation [lxxi]. It also exerts powerful inhibitory effect against hydrogen peroxide-induced damage in human keratinocytes and fibroblasts [lxxii]. In addition, curcumin, chief constituents of turmeric shows role in the improvement of the activities of detoxifying enzymes such as glutathione-S-transferase (GST) [lxxiii]. Earlier study reported that curcumin efficiently inhibits intracellular amyloid toxicity at low dosages based on rats through its free radical scavenging activity [lxxiv]. Experiment based on rat model confirmed that oral administration of curcumin showed noteworthy reversal in lipid peroxidation, brain lipids as well as produced enhancement of glutathione [lxxv].

3. Anti-inflammatory activity

A study based on animal model, curcumin inhibited arachidonic acid metabolism and inflammation in skin epidermis through down regulation of the pathways of cyclooxygenase and lipoxygenase [lxxvi].

Previous studies have shown its effect in the reduction of neutrophil infiltration in inflammatory conditions [lxxvii, lxxviii, lxxix]. Other results showed that curcumin inhibited arthritis at a dose of 40 mg/kg, and acute toxicity was not noticed at doses up to 2 g/kg body weight [lxxx]. Earlier finding has shown that curcumin exerts its anti-inflammatory effects in murine colitis models via inhibition of COX-2-and pro-inflammatory cytokine expression [lxxxi, lxxxii, lxxxiii] and suppression of nuclear factor kappa B (NF-κB)activation [lxxxiv, lxxxv]. Curcumin, shows a role in the suppression of both acute and chronic inflammation as it block the formation of enzymes such as COX-2 involved in inflammation [lxxxvi]. Curcumin supplementation is linked with lowered plasma levels of tumour necrosis factor-alpha (TNF-α), interleukin-6, and monocyte chemoattractant protein-1 in diabetic rats and in high glucose treated monocytes [lxxxvii].

4. Immunomodulatory Activity

A study was performed to check the effect of curcumin on T, B cells and macrophages and results showed that curcumin imparted immunosuppression by mainly down-regulating the expression of CD28 and CD80 and up-regulating cytotoxic T-lymphocyte antigen 4 (CTLA-4) [lxxxviii]. Other study confirmed that curcumin inhibited the proliferation induced by concanavalin A, phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate of lymphocytes derived from fresh human spleen [lxxxix, xc]. Experiment results noticed that curcumin inhibits PHA-induced T-cell proliferation, interleukin-2 production, NO generation, and lipopolysachharide-induced NF-κB and augments NK cell cytotoxicity [xci]. Numerous previous results have shown curcumin as immunomodulatory that shows an important effect in the modulation of activation of T cells, B cells, macrophages, dendritic cells, cell cycle protein, cell-mediated and humoral mediated immunity [xcii, xciii, xciv].

6. *Matulunga* (*Citrus medica*)

1. Antioxidant Activity

Citrus fruits are reported to have a good anti-oxidant ability especially because of their phenolic compounds with poly-hydroxyl groups, including phenolic acids, flavonoids and their derivatives [xcv]. The primary anti-oxidant mechanisms of phenolic compounds are direct absorption and neutralization of free radicals [xcvi], inhibition of enzymes associated with ROS pathways-NADPH oxidase, xanthine oxidase and myeloperoxidase [xcvii], enhancement of the activities of human anti-oxidant enzymes- superoxide dismutase, catalase, etc [xcviii].

2. Anti-Inflammatory Activity

Flavonoids, coumarin and volatile oil from Citrus fruit are showing anti-inflammatory activity, which can be used as supplement to protect against or ameliorate these chronic inflammatory diseases [xcix].

3. Anti-Carcinogenic Activity

Citrus fruits are high in secondary metabolites, including flavonoids, limonoids, and coumarins, which are associated with a reduced risk of cancer, including gastric cancer, breast cancer, lung tumorigenesis, colonic tumorigenesis, hepatocarcinogenesis, and hematopoietic malignancies, etc.

DISSCUSSION

Sneha Murchana is the first step towards any *Sneha paka* process. It is a special pharmaceutical procedure before subjecting the drugs to *Sneha paka*. For the Preliminary treatment of *ghrita* (refining of *ghrita*) six herbal drugs are added to it. These herbal drugs are: *Haritki* (*Terminalia chebula*), *Amalaki* (*Emblica officinalis*), *Vibhitaki* (*Terminalia bellirica*), *Mustaka* (*Cyperus rotundus*), *Haridra* (*Curcuma longa*), *Matulunga* (*Citrus medica*). Alcoholic extract of dried ripe fruit of *Terminalia chebula* was found to increase liver mitochondrial enzymes (CAT&SO) as well as GSH but decreased level of LPO in liver. It Increases secretion of melatonin by pineal gland. The extract also increases spleen lymphocyte proliferation. It increases the expression of cytokines IL-2, IL-10, TNF-α. It also increases leucocyte count (DLC), phagocytic activity and immunoglobulin level. Oral administration of alcoholic extract at a dose of 100mg/kg was found to increase neutrophils and lymphocytes. Antioxidant activity of ethanolic extract of fruits at dose of 500 mg/kg body wt. orally for 30 days and 200mg/kg body wt. for 30 days have been studied and found effective. Different antioxidants of the extracts exhibit anti-inflammatory and immunosuppressive properties also by neutralizing Reactive oxygen species (ROS) and scavenging free radicals. The free radicals are responsible for causing inflammation by stimulating release of cytokines such as IL-1, TNF-α, and IFN-β which stimulate additional neutrophils and macrophages at the site of inflammation.The anti-oxidant activity of methanol extract, aqueous extract, hexane extract, petroleum ether, benzene, chloroform and ethyl acetate have also been proved. The anti-oxidant activity of methanolic extract was directly proportional to the amount of total phenols. Aqueous extract decreases the age related oxidative stress in heart tissue of rats. Aqueous extract at a dose of 500mg/kg orally increases the WBC, lymphocyte and delayed type hypersensitivity response. Gallic acid and Chebulagic acid isolated from the extract are the active principles responsible for blocking the other biologically active compounds make it a highly potent anti-oxidant which may be responsible for its immunomodulatory activity. Ethanolic extract of *Terminalia bellirica* at a dose of 350mg/kg improves the delayed type hypersensitivity response, improves the protection against cyclophosphamide induced neutropenia. Also causes significant increase in weight of spleen. Acetone extract has mild inhibitory effect on generation of oxidase enzyme during phagocytosis. It stimulates proliferation of B and T lymphocytes. Reduces production of IFN-y and IL-2 but increases IL-10 secretion. Gallic acid may contribute to the immunomodulatory activity of *Terminalia bellirica* fruits as it presents similar effects as *T.bellirica* extract. Ethyl acetate extract of Amla has antioxidant efficacy and can be used in age-related Renal diseases. It reduces the elevated levels of Urea Nitrogen and serum creatinine in aged rats. It significantly reduces thiobarbituric acid reactive substances, also reduces COX-2, nitric oxide synthetase expression by inhibiting NF kappa β activation in aged rats. Pre feeding of Amla elevates hepatic anti-oxidant system and lowers cytotoxic products. It relives oxidative stress and improves glucose metabolism in diabetes.Amla extract has strong free radical scavenging activity, improves weight, improves albumin level, improves serum adiponectin levels in diabetic rats. It contains tannoid principles comprising of Emblicanin A, Emblicanin B, Punigluconin, Pedunculagin. These have ascorbic acid like action. Emblicanin A and Emblicanin B have cardioprotective effect also. Ellagic acid is a powerful antioxidant and can inhibit mutation in genes and repair chromosomal abnormalities. It can relieve immunosuppressive effect of chromium on lymphocyte Proliferation and restores IL-2 and gamma IFN production.Emblicanin A and B have anti-cancer properties also. It inhibits growth and spread of various cancers. Enhances NK cell activity in various tumours.Increases life span of tumour bearing animals.The protection provided by *E.officinalis* fruit may also be due to its immunomodulatory effect on hepatic activation and detoxifying enzymes. *E.Officinalis* polyphenol fraction decreases the liver tumour development. It decreases elevated levels of liver enzymes (GPT, ALP, GST, GSH). It scavenges superoxide and hydroxyl radicals and inhibits lipid peroxidation.It also inhibits DNA topoisomerase 1 in saccharomyces cervisiae mutant cell cultures and activity of cdc 25 tyrosine phosphatase. Aqueous extract has the ability of stimulating humoral as well as cell mediated immunity. Its tannins showed immunostimulatory property (increased body weight, high antibody titres, low caecal and intestinal lesions) in Broilers against Emeria infection. The Ethanolic extract of roots and

rhizome of *Cyperus rotundus* show anti-oxidant activity. It contains potent flavonoids responsible for modulating immune system, analgesic, anti-inflammatory and anti-oxidant effect.*C.rotundus* reduces CD4 and CD8 T cells. CD11b cell macrophages are also reduced. TNF-α,IFN-γ,IL-1β and IL-6 levels are also suppressed which marks its anti-inflammatory effect. Curcumin at a dose of 8g/day has shown chemo and radio protective properties. At a dose of 12g/day it can be used to treat patients of multiple myeloma. At a dose of 1.5g/day given in chronic smokers, it decreased urinary mutagens with no changes in AST, ALT, Blood glucose, creatinine or lipid profile. Hence curcumin can be used as a dietary modification to decrease the risk of lung cancer. It may also play a role in suppressing production of PSA (prostate specific antigen).It is a effective scavenger of ROS and reactive nitrogen species. It controls DNA damage and lipid peroxidation, making it a potent anti-oxidant substance. It has powerful inhibitory effect against hydrogen peroxide induced damage in keratinocytes and fibroblasts. It helps in improvement of activities of detoxifying enzymes such as Glutathione-S-transferase (GST). Curcumin shows role in suppression of both acute and chronic inflammation as it blocks the formation of enzymes such as Cox-2, reduces neutrophil infilteration and pro-inflammatory cytokinin expression (TNF-α, IL-6, IL-2) and suppression of NF-Kβ (Nuclear factor Kappa β) activation. It also down regulates expression of CD 28 and CD80 and up regulates cytotoxic T lymphocyte antigen 4.It inhibits T cell proliferation, NO generation, augments NK cell toxicity. Citrus substances are good antioxidants because of their phenolic compounds with poly hydroxyl groups including phenolic acids, flavonoids and their derivatives. The primary anti-oxidant mechanisms of phenolic compounds are direct absorption and neutralization of free radicals, inhibition of enzymes associated with ROS pathways-NADPH oxidase, xanthine oxidase and myeloperoxidase, enhancement of the activities of human anti-oxidant enzymes- superoxide dismutase, catalase, etc. Flavonoids, coumarin and volatile oil from Citrus fruit have anti-inflammatory activity, which can be used as supplement to protect against or ameliorate the chronic inflammatory diseases. Citrus fruits being high in secondary metabolites, including flavonoids, limonoids, and coumarins, are associated with a reduced risk of cancer, including gastric cancer, breast cancer, lung tumorigenesis, colonic tumorigenesis, hepatocarcinogenesis, and hematopoietic malignancies, etc.

CONCLUSION

The above collected information suggest that these six *Murchana* herbs have anti-oxidant, anti-inflammatory, anti-carcinogenic, analgesic and immunomodulatory activity. Hence it can be concluded that along with other benefits such as imparting good smell and colour to ghee, increasing the potency of ghee, making ghee imbibe more active principles from the drug with which it is processed, increasing its solubility , absorption and potency of the finished product, removal of '*Ama'* which can be correlated to the 'moisture content' which can be directly related to rancidity problems, refining *Murchana* process of *ghrita* might also be responsible for increasing the immunostimulant potential of Cow's ghee.

[i] Sen Govind das, Bheshajratnavali, Hindi commentary by Misra Siddhinandan, edition 2015, Chaukhamba Surbharati prakashan, Chapter-5, pg. 206

[ii] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.753

[iii] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.236

[iv] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.758

[v] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.162

[vi] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.370

[vii] Sharma P.V, Dravyagun vigyan,Chaukhamba Bharti Academy,edition 1988, p.343

[viii] Upadhyay, A., Agrahari, P., & Singh, D. K. (2014). A review on the pharmacological aspects of Terminalia chebula. *Int. J. Pharmacol*, *10*(6), 289-298.

[ix] Kumari, S., Mythili Krishna, J., Joshi, A. B., Gurav, S., Bhandarkar, A. V., Agarwal, A., ... & Gururaj, G. M. (2017). A pharmacognostic, phytochemical and pharmacological review of Terminalia bellerica. *Journal of Pharmacognosy and Phytochemistry*, *6*(5), 368-376.

[x] Charmkar, N. K., & Singh, R. (2017). Emblica officinalis Gaertn. (Amla): a wonder gift of nature to humans. *Int. J. Curr. Microbiol. App. Sci*, *6*(7), 4267-4280.

[xi] Sivapalan, S. R. (2013). Medicinal uses and pharmacological activities of Cyperus rotundus Linn-A Review. *International Journal of Scientific and Research Publications*, *3*(5), 1-8.

[xii] Gupta Sandeep, K. (2010). Phytochemistry of curcuma longa: An overview. *Journal of Pharmaceutical and Biomedical Sciences.* 4 (01).

[xiii] Meena,AK et al. (2011).A Review On Citron-Pharmacognosy, Phytochemistry and Medicinal Uses. *International Research Journnal of Pharmacy*.2 (1). 14-19.

[xiv]Aher, V., & Wahi, A. (2011). Immunomodulatory activity of alcohol extract of Terminalia chebula retz combretaceae. *Tropical Journal of Pharmaceutical Research*, *10*(5), 567-575.

[xv] Shivaprasad HN, Kharya MD, Rana AC, Mohan S. Preliminary immunomodulatory activities of the aqueous extract of *Terminalia chebula*. Pharm Biol., 2006; 44: 32–4.

[xvi] Khan KH. Immunomodulatory activity of *Terminalia chebula* against *Salmonella typhimurium* in mice. Recent Res Sci Tech., 2009; 1: 211–6.

[xvii] Antioxidant effects of aqueous extract of Terminalia chebula in vivo and in vitro. *Lee HS, Won NH, Kim KH, Lee H, Jun W, Lee KW Biol Pharm Bull., 2005 Sep; 28(9): 1639-44*

[xviii] Isolation of chebulic acid from Terminalia chebula Retz. and its antioxidant effect in isolated rat hepatocytes. *Lee HS, Jung SH, Yun BS, Lee KW Arch Toxicol, 2007 Mar; 81(3): 211-8.*

[xix] Antioxidant, antihypertensive, and antibacterial properties of endophytic Pestalotiopsis species from medicinal plants. *Tejesvi MV, Kini KR, Prakash HS, Subbiah V, Shetty HS Can J Microbiol, 2008 Sep; 54(9): 769-80.*

[xx] Conforti F, Sosa S, Marrelli M, Menichini F, Statti GA, Uzunov D. The protective ability of Mediterranean dietary plants against the oxidative damage: The role of radical oxygen species in inflammation and the polyphenol, flavonoid and sterol contents. Food Chem., 2009; 112: 587–94.

[xxi] Vaibhav D Aher. Immunomodulatory effect of alcoholic extract of Terminalia chebula ripe fruits, J. Pharm. Sci. & Res. Vol.2 (9), 2010, 539-544.

[xxii] Chang, C. L., & Lin, C. S. (2010). Development of antioxidant activity and pattern recognition of Terminalia chebula Retzius extracts and its fermented products. *HungKuang J*, *61*, 115-129.

[xxiii] Hua-Yew CHENG. Antioxidant and Free Radical Scavenging Activities of *Terminalia chebula*, *Biol. Pharm. Bull.* 2003, 26(9) 1331—1335.

[xxiv] Harpreet, W., Subodh, K., & Saroj, A. (2011). Comparative antioxidant analysis of hexane extracts of Terminalia chebula Retz. prepared by maceration and sequential extraction method. *Journal of Medicinal Plants Research*, *5*(13), 2608-2616.

[xxv] Penpun Wetwitayaklung. Antioxidant Activities of Some Thai and Exotic Fruits Cultivated in Thailand, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2012, 3(1), 12.

[xxvi] Ramalingam Mahesh and Vava Mohaideen Hazeena Begum, Antioxidant Effect of *Terminalia chebula*Aqueous Extract on Age-related Oxidative Stress in Heart, Iranian Journal of Pharmacology &Therapeutics, 2007, 6, 197-201.

[xxvii] Singh Veena. D and Mishra R.N., *In-Vitro* Antioxidant Activity of Megaext of Triamrit, International Journal Of Research In Pharmacy And Chemistry, 2011, 1(1), 36-39.

[xxviii] Naik G. H., Indira Priyadarsini, K. and Hari Mohan, Evaluating the antioxidant activity of different plant extracts and herbal formulations, *Res. Chem. Intermed*., 2005, 31(1–3), pp. 145–151.

[xxix] Bibhabasu Hazra et al, RCesoeamrchp Artaicrleative study of the antioxidant and reactive oxygen species scavenging properties in the extracts of the fruits of Terminalia chebula, Terminalia belerica and Emblica officinalis, *BMC Complementary and Alternative Medicine* 2010, 10:20.

[xxx] Subramaniyan Suchalatha and Chennam Srinivasulu Shyamala Devi, *Indian Journal of Biochemisty &Biophysics*, 2005, 42, 246-249.

[xxxi] Senthilkumar GP. Evaluation of Antioxidant Potential of Terminalia chebula Fruits Studied in Streptozotocin-Induced Diabetic Rats. Pharmaceutical Biology, 2007, 45, 511-518.

[xxxii] Hamada S, Kataoka T, Woo JT, Yamada A, Yoshida T, Nishimura T, Otake N, Nagai K. Immunosuppressive effects of gallic acid and chebulagic acid on CTLmediated cytotoxicity. *Biol PharmBull.* 1997, 20, 1017-9.

[xxxiii] Manjunatha, M., Bhalodiya, H., Ansari, M. A., Vadaand, S., & Goli, D. (2011). Immunomodulatory activity of Terminalia bellirica extract in mice. *Phytochemical Analysis*, *8*, 9.

[xxxiv] Saraphanchotiwitthaya, A. U. R. A. S. O. R. N., & Ingkaninan, K. O. R. N. K. A. N. O. K. (2014). Immunomodulatory activity of an acetone extract of Terminalia bellerica Roxb fruit on the mouse immune response in vitro. *Int. J. Pharm. Pharm. Sci*, *6*, 274-278.

[xxxv] Yokozawa T, Kim HY, Kim HJ, Okubo T, Chu DC, Juneja LR.Amla (*Emblica officinalis* Gaertn.) prevents dyslipidaemia and oxidative stress in the ageing process. Br J Nutr 2007; 97(6):1187-1195.

[xxxvi] Anilakumar KR, Nagaraj NS, Santhanam K. Reduction of hexachlorocyclohexane-induced oxidative stress and cytotoxicity in rat liver by *Emblica officinalis* Gaertn. Indian J Exp Biol 2007; 45(5):450-454.

[xxxvii] Rao TP, Sakaguchi N, Juneja LR, Wada E, Yokozawa T. Amla (*Emblica officinalis* Gaertn.) extracts reduce oxidative stress in streptozotocin induced diabetic rats. J Med Food 2005; 8(3): 362-368.

[xxxviii] Chaudhuri RK. *Emblica* cascading antioxidant: A novel natural skin care ingredient. Skin Pharmacol Appl Skin Physiol 2002; 15(5):374-380.

[xxxix] Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Effect of bioactive tannoid principles of *Emblica officinalis* on ischemiareperfusion induced oxidative stress in rat heart. Phytomedicine 2002; 9(2):171-174.

[xl] Pozharitskaya ON, Ivanova SA, Shikov AN, Makarov VG. Separation and evaluation of free radical-scavenging activity of phenol components of *Emblica officinalis* extract by using an HPTLC-DPPH method. J Sep Sci 2007; 30(9):1250-1254.

[xli] Bhattacharya A, Ghosal S, Bhattacharya SK. Antioxidant activity of tannoid principles of *Emblica officinalis* (amla) in chronic stress induced changes in rat brain. Indian J Exp Biol 2000; 38(9):877-880.

[xlii] Pandey Govind. Some important anticancer herbs: A review. Int Res J Pharm 2011; 2(7):45-52.

[xliii] Sai Ram M, Neetu D, Yogesh B, Anju B, Dipti P, Pauline T,Sharma SK, Sarada SK, Ilavazhagan G, Kumar D, Selvamurthy W. Cyto-protective and immunomodulating properties of Amla (*Emblica officinalis*) on lymphocytes: An *in-vitro* study. J Ethnopharmacol 2002; 81(1):5-10.

[xliv] Sai Ram M, Neetu D, Dipti P, Vandana M, Ilavazhagan G, Kumar D, Selvamurthy W. Cytoprotective activity of Amla(*Emblica officinalis*) against chromium (VI) induced oxidative injury in murine macrophages. Phytother Res 2003; 17(4):430-433.

[xlv] Singh, M. K., Yadav, S. S., Gupta, V., & Khattri, S. (2013). Immunomodulatory role of Emblica officinalis in arsenic induced oxidative damage and apoptosis in thymocytes of mice. *BMC Complementary and Alternative Medicine*, *13*(1), 1-13.

[xlvi] Ganju L, Karan D, Chanda S, Srivastava KK, Sawhney RC, Selvamurthy W. Immunomodulatory effects of agents of plant origin. Biomed Pharmacother 2003; 57(7):296-300.

[xlvii] Arondekar S. Studies on central actions of *Withania somnifera* with special reference to its immunomodulatory effect in albino rats. MVSc & AH thesis. Jabalpur, MP: JNKVV; 1999.

[xlviii] Banu SM, Selvendiran K, Singh JP, Sakthisekaran D. Protective effect of *Emblica officinalis* ethanolic extract

against 7, 12- dimethylbenz(a) anthracene (DMBA) induced genotoxicity in Swiss albino mice. Hum Exp Toxicol 2004; 23(11):527-531.

[xlix] Haque R, Bin-Hafeez B, Ahmad I, Parvez S, Pandey S, Raisuddin S. Protective effects of *Emblica officinalis* Gaertn. In cyclophosphamide treated mice. Hum Exp Toxicol 2001; 20(12): 643-650

[l] Rajani, J., Ashok, B. K., Galib, B. J., Prajapati, P. K., & Ravishankar, B. (2012). Immunomodulatory activity of Āmalaki Rasāyana: An experimental evaluation. *Ancient science of life*, *32*(2), 93.

[li] Suja, R. S., Nair, A. M. C., Sujith, S., Preethy, J., & Deepa, A. K. (2009). Evaluation of immunomodulatory potential of Emblica officinalis fruit pulp extract in mice. *Indian Journal of Animal Research*, *43*(2), 103-106.

[lii] Kaleem, Q. M., Akhtar, M., Awais, M. M., Saleem, M., Zafar, M., Iqbal, Z., ... & Anwar, M. I. (2014). Studies on Emblica officinalis derived tannins for their immunostimulatory and protective activities against coccidiosis in industrial broiler chickens. *The Scientific World Journal*, *2014*.

[liii] Nandi P, Talukder G, Sharma A. Dietary chemoprevention ofclastogenic effects of 3,4-benzo(a)pyrene by *Emblica officinalis* Gaertn. fruit extract. Br J Cancer 1997; 76(10):1279-1283.

[liv] Zhang YJ, Nagao T, Tanaka T, Yang CR, Okabe H, Kouno I. Antiproliferative activity of the main constituents from *Phyllanthus emblica.* Biol Pharm Bull 2004; 27(2):251-255.

[lv] Madhuri S. Studies on oestrogen induced uterine and ovarian carcinogenesis and effect of ProImmu in rat. PhD thesis. Jabalpur, MP: RDVV; 2008.

[lvi] Sancheti G, Jindal A, Kumari R, Goyal PK. Chemopreventive action of *Emblica officinalis* on skin carcinogenesis in mice. Asian Pac J Cancer Prev 2005; 6(2):197-201.

[lvii] Rajeshkumar NV, Pillai MR, Kuttan R. Induction of apoptosis in mouse and human carcinoma cell lines by *Emblica officinalis* polyphenols and its effect on chemical carcinogenesis. J Exp Clin Cancer Res 2003; 22(2):201-212.

[lviii] Khan MT, Lampronti I, Martello D, Bianchi N, Jabbar S, Choudhuri MS, Datta BK, Gambari R. Identification of pyrogallol as an antiproliferative compound present in extracts from the medicinal plant *Emblica officinalis*: Effects on *in vitro* cell growth of human tumor cell lines. Intl J Oncol 2002; 21(1):187-192.

[lix] Pal, D. K., & Dutta, S. (2006). Evaluation of the Antioxidant activity of the roots and Rhizomes of Cyperus rotundus L. *Indian journal of Pharmaceutical sciences*, *68*(2).

[lx] Soumaya, K. J., Dhekra, M., Fadwa, C., Zied, G., Ilef, L., Kamel, G., & Leila, C. G. (2013). Pharmacological, antioxidant, genotoxic studies and modulation of rat splenocyte functions by Cyperus rotundus extracts. *BMC Complementary and Alternative Medicine*, *13*(1), 1-11.

[lxi] Ramadhani, A. H., Nafisah, W., Isnanto, H., Sholeha, T. K., Jatmiko, Y. D., Tsuboi, H., & Rifa'i, M. (2020). Immunomodulatory Effects of Cyperus rotundus Extract on 7, 12 Dimethylbenz [a] anthracene (DMBA) Exposed BALB/c Mice. *Pharmaceutical Sciences*, *27*(1), 46-55.

[lxii] Epelbaum R, Schaffer M, Vizel B, Badmaev V, Bar-Sela G. Curcumin and gemcitabine in patients with advanced pancreatic cancer. Nutr Cancer. 2010 Nov;62:1137e1141.

[lxiii] Gupta Subash C, Patchva Sridevi, Aggarwal Bharat B. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2012;15(1):195e218.

[lxiv] Ravindranath V, Chandrasekhara N. Metabolism of curcumindstudies with [3H]curcumin. Toxicology. 1982;22(no. 4):337e344.

[lxv] Zhou D, Ding N, Du Z, et al. Curcumin analogues with high activity for inhibiting human prostate cancer cell growth and androgen receptor activation. Mol Med Rep Mol Med Rep. 2014;10(3):1315e1322.

[lxvi] Bayet-Robert M, Morvan D. Metabolomics reveals metabolic targets and biphasic responses in breast cancer cells treated by curcumin alone and in association with docetaxel. PLoS One. 2013;8(3).

[lxvii] Gupta S, Patchva S, Aggarwal B. Therapeutic roles of curcumin: lessons learned from clinical trials. APPS J. January 2013;15(No 1).

[lxviii] Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoids. *J Pharm Pharmacol.* 1997;49:105–7.[PubMed: 9120760]

[lxix] Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. *Arzneimittelforschung.*1996;46:169–71. [PubMed: 8720307]

[lxx] Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A, Uno H. On the antioxidant mechanism of curcumin: Classical methods are needed to determine antioxidant mechanism and activity.*Org Lett.* 2000;7(2) 18:2841–3. [PubMed: 10964379]

[lxxi] Shukla PK, Khanna VK, Khan MY, Srimal RC. Protective effect of curcumin against lead neurotoxicity in rat. *Hum Exp Toxicol.* 2003;22:653–8. [PubMed: 14992327]

[lxxii] Phan TT, See P, Lee ST, Chan SY. Protective effects of curcumin against oxidative damage on skincells *in vitro*: Its implication for wound healing. *J Trauma.* 2001;51:927–31. [PubMed: 11706342]

[lxxiii] Piper JT, Singhal SS, Salameh MS, Torman RT, Awasthi YC, Awasthi S. Mechanisms ofanticarcinogenic properties of curcumin: The effect of curcumin on glutathione linked detoxificationenzymes in rat liver. *Int J Biochem Cell Biol.* 1998;30:445–56. [PubMed: 9675878]

[lxxiv] Ye J, Zhang Y. Curcumin protects against intracellular amyloid toxicity in rat primary neurons. *Int JClin Exp Med.* 2012;5:44–9. [PMCID: PMC3272685] [PubMed: 22328947]

[lxxv] Rajakrishnan V, Viswanathan P, Rajasekharan KN, Menon VP. Neuroprotective role of curcumin from*Curcuma longa* on ethanol-induced brain damage. *Phytother Res.* 1999;13:571–4. [PubMed: 10548748]

[lxxvi] Huang MT, Lysz T, Ferraro T, Abidi TF, Laskin JD, Conney AH. Inhibitory effects of curcumin on *invitro* lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res.* 1991;51:813–9.[PubMed: 1899046]

[lxxvii] Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni JR, Das PK. Curcumin, the major component offood flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. *Br JPharmacol.* 2003;139:209–18. [PMCID: PMC1573841] [PubMed: 12770926]

[lxxviii] Lukita-Atmadja W, Ito Y, Baker GL, McCuskey RS. Effect of curcuminoids as anti-inflammatoryagents on the

hepatic microvascular response to endotoxin. *Shock.* 2002;17:399–403. [PubMed: 12022761]

[lxxix] Gukovsky I, Reyes CN, Vaquero EC, Gukovskaya AS, Pandol SJ. Curcumin ameliorates ethanol andnonethanol experimental pancreatitis. *Am J Physiol Gastrointest Liver Physiol.* 2003;284:G85–95.[PubMed: 12488237]

[lxxx] Srimal RC, Dhawan BN. Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *J Pharm Pharmacol.* 1973;25:447–52. [PubMed: 4146582]

[lxxxi] Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M, Nagata T. Curcumin prevents andameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology.* 2002;123:1912–22.[PubMed: 12454848]

[lxxxii] Camacho-Barquero L, Villegas I, Sánchez-Calvo JM, Talero E, Sánchez-Fidalgo S, Motilva V. Curcumin, a *Curcuma longa* constituent, acts on MAPK p38 pathway modulating COX-2 and iNOSexpression in chronic experimental colitis. *Int Immunopharmacol.* 2007;7:333–42. [PubMed: 17276891]

[lxxxiii] Ung VY, Foshaug RR, MacFarlane SM, Churchill TA, Doyle JS, Sydora BC. Oral administrationof curcumin emulsified in carboxymethyl cellulose has a potent anti-inflammatory effect in the IL-10gene-deficient mouse model of IBD. *Dig Dis Sci.* 2010;55:1272–7. [PubMed: 19513843]

[lxxxiv] Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. *J Immunol.* 1999;163:3474–83. [PubMed: 10477620]

[lxxxv] Jian YT, Mai GF, Wang JD, Zhang YL, Luo RC, Fang YX. Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid. *World J Gastroenterol.*2005;11:1747–52. [PMCID: PMC4305867] [PubMed: 15793857]

[lxxxvi] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent,against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *IntJ Biochem Cell Biol.* 2009;41:40–59. [PMCID: PMC2637808] [PubMed: 18662800]

[lxxxvii] Jain SK, Rains J, Croad J, Larson B, Jones K. Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6,MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. *Antioxid Redox Signal.* 2009;11:241–9.[PMCID: PMC2933148] [PubMed: 18976114]

[lxxxviii] Sharma S, Chopra K, Kulkarni SK, Agrewala JN. Resveratrol and curcumin suppress immune responsethrough CD28/CTLA-4 and CD80 co-stimulatory pathway. *Clin Exp Immunol.* 2007;147:155–63.[PMCID: PMC1810449] [PubMed: 17177975]

[lxxxix] Javvadi P, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potentradiosensitizer of human cervical tumor cells via increased reactive oxygen species production andoveractivation of the mitogen-activated protein kinase pathway. *Mol Pharmacol.* 2008;73:1491–501.[PMCID: PMC3400533] [PubMed: 18252805]

[xc] Ranjan D, Chen C, Johnston TD, Jeon H, Nagabhushan M. Curcumin inhibits mitogen stimulatedlymphocyte proliferation, NFkappaB activation, and IL-2 signaling. *J Surg Res.* 2004;121:171–7.[PubMed: 15501456]

[xci] Yadav VS, Mishra KP, Singh DP, Mehrotra S, Singh VK. Immunomodulatory effects of curcumin.*Immunopharmacol Immunotoxicol.* 2005;27:485–97. [PubMed: 16237958]

[xcii] Gautam SC, Gao X, Dulchavsky S. Immunomodulation by curcumin. *Adv Exp Med Biol.*2007;595:321–41. [PubMed: 17569218]

[xciii] Gao X, Kuo J, Jiang H, Deeb D, Liu Y, Divine G. Immunomodulatory activity of curcumin:Suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokineproduction *in vitro*. *Biochem Pharmacol.* 2004;68:51–61. [PubMed: 15183117]

[xciv] Kim GY, Kim KH, Lee SH, Yoon MS, Lee HJ, Moon DO. Curcumin inhibits immunostimulatoryfunction of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. *J Immunol.*2005;174:8116–24. [PubMed: 15944320]

[xcv] Hirata T, Fujii M, Akita K, Yanaka N, Ogawa K, Kuroyanagi M, Hongo D (2009) Identification and physiological evaluation of the components from Citrus fruits as potential drugs for anti-corpulence and anticancer. Bioorgan Med Chem 17:25–28

[xcvi] Osawa T (1994) Novel natural antioxidants for utilization in food and biological systems. In: Uritani I, Garcia VV, Mendoza EM (eds) Postharvest biochemistry of plant food-materials in the tropics. Japan Scientific Societies Press, Japan, pp 241–251

[xcvii] Cotelle N (2001) Role of flavonoids in oxidative stress. Curr Top Med Chem 1:569–590

[xcviii] Mari M, Colell A, Morales A, von Montfort C, Garcia-Ruiz C, FernandezCheca JC (2010) Redox control of liver function in health and disease. Antioxid Redox Sign 12:1295–1331

[xcix] Lv, X., Zhao, S., Ning, Z., Zeng, H., Shu, Y., Tao, O., Xiao, C., Lu, C., & Liu, Y. (2015). Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. *Chemistry Central journal*, *9*, 68. https://doi.org/10.1186/s13065-015-0145-