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Lelmmune-T

Natural Killer Cells mediated

Innate Immunity Booster for

improving/restoring activity of Natural Killer Cells/Innate Immunity against any virus – including Novel Coronavirus

We have released a Natural Killer Cells mediated Innate Immunity Booster made from Tomato by name “Lelmmune-T”.

Regulatory position of Lelmmune-T:

Regulations applicable to Lelmmune -T are:

(A) Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016 (“The Regulation A”, hereafter).

“Lelmmune-T” is an extract of tomato in edible oil containing at least 418 µg bioavailable β-carotene dissolved in edible oil, is a Nutraceutical listed at No. 164 in Schedule VI of The Regulation A. It may further contain permitted additives.

(B) Food Safety and Standards (Advertising and Claims) Regulations, 2018 (“The Regulation B”, hereafter)

Lelmmune-T, is labeled with a β-carotene-led (ingredient-led)a claim “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells” which reads as follows:

“There is Significant Scientific Agreement that beta carotene improves/restores activity of Natural Killer Cells activity in Innate Immunity compromised persons. Daily consumption of 200 g purple sweet potato leaves containing 23.42 mg β-Carotene improved the lytic activity of Natural Killer cells within 15 days in a human clinical trial

(Chen et al.; World J Gastroenterol October 7, 2005 Volume 11 Number 37). From 56 molecules contained in green leafy vegetables, 1 molecule of beta carotene (that gives two molecules of Vitamin A) is bioavailable (GuangwenTang 2010; Am J Clin Nutr 2010;91(suppl):1468S–73S. Provitamin A carotenoids conversion factors (on a weight basis) is 28:1 with leafy vegetables). Thus, daily consumption of 418 µg of bioavailable β-Carotene improved the lytic activity of Natural Killer cells within 15 days in average individual.

Accordingly, “Lelmmune-T”, an oil extract of tomato with at least 418 microgram of bioavailable beta-carotene in 5 ml. improves/restores activity of Natural Killer Cells/Innate Immunity (the First Line Immunity) capable destroying, without the need of prior vaccination, of destroying cells infected by any virus [Novel Coronavirus (SARS-CoV-2) is a virus], bacteria and initial stage solitary cancer cells before that pathogen.cancer cell gets an opportunity to multiply to give rise to the disease.”

Regulatory position of the label claim of Lelmmune-T “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells” :

(A) Under Regulation A: This label claim complies with the sub-regulation (8)(i)(ii)(v)(v) which is recited in The Regulation A as follows:

(8) To claim **ingredients**, nutrient or nutritional, **in respect of** an article of food for **enhanced function** and disease risk reduction, regard shall be had to-

- (i) claims that led to **ingredients** (nutrient or nutritional);
- (ii) **available scientific literature** including official traditional texts and post market data or consumer studies or cohort or **retroactive studies based on eating pattern and health benefits, epidemiological international and national data, and other well documented data;**
- (iii) consensual, congruent and concurrent validity studies;
- (iv) health promotive and disease risk reduction based on proof from literature and human data of efficacy and safety of the nutrient;
- (v) not only controlled clinical trials for efficacy and safety data; but also **nutraepidemiological** data.

(B) Under Regulation B: This label claim complies with the “other function claim” defined under definition (h) as:

“(ii) “other function claim” that describes the specific beneficial effects of the

consumption of foods or their constituents, in the context of the total diet or normal functions or biological activities of the body, which relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health.”;

which is required to comply with sub-regulation 7(2) recited as follows:

“(2) Nutrient function claims and other function claims may be made based on current relevant scientific substantiation and to provide sufficient evidence on the type of claimed effect and the relationship to health as recognised by generally accepted scientific review of the data and the scientific substantiation shall be reviewed by food business operator as new knowledge becomes available and claims updated accordingly.”

The Clinical Nutritional merit and current relevant scientific substantiation and to provide sufficient evidence on the type of claimed effect and the relationship to health as recognised by generally accepted scientific review of the data on LeImmune-T “improves/restores activity of Natural Killer Cells/Innate Immunity capable of killing cells infected by any virus (Novel Coronavirus is a virus), bacteria and initial stage cancer cells”:

The Clinical Nutritional merit:

Unique importance of Innate Immunity as the only means that enables breaking chain of infections when absolute enforcement of social distancing is not fully efficacious: During the first critical hours and days of exposure to a new pathogen, we rely ONLY on our Innate Immune system to protect us from infection (<https://www.ncbi.nlm.nih.gov/books/NBK26846/>).

Here the term “Innate Immunity system” refers to “Natural Killer Cells mediated Innate Immune System” which is also known as “Non-specific” immunity, which does not require a vaccination or a prior exposure to a pathogenic virus to detect a cell infected by that virus and to apoptize (kill with all the nucleic acid content) a virus infected cell.

This explains the mechanism of spread of any infectious viral disease. Those who have their Innate Immunity at optimum level have least probability to develop the disease even if they come in contact with a virus against which they are NOT vaccinated, because the very first batch of cells infected by the virus will be detected by the Natural Killer Cells and destroyed totally with genetic material of the virus contained in the cell (apoptized) within first few hours

before the genetic material of the virus gets a chance to multiply and spread in the body of that person. Additionally, it may also serve as a “Natural vaccination”, because, in the meanwhile, the Adaptive Immunity System of that person would have got exposure to that virus and within a couple of days, it would develop antibodies in such a person without an artificial vaccine injection to him.

Hence, Innate Immunity merits attention as a First Line of Action for control of a pandemic.

It is only that group of persons would get the disease after the initial infection in whom the Natural Killer Cells have reduced their activity. The result is that the virus does not get killed in the first go, gets time to multiply and spread in the body of that person. If the activity of Natural killer cells, in such an Immune Compromised person is just below its optimum, then while it will try its best to destroy as many of the multiplied viruses as possible, in first couple of days with whatever is its lowered capability, within a few days, the antibodies made by the Adaptive Immune System also comes as supply of fresh fighters against the virus, and slowly the balance of fight tips against the virus load in the body and the patient recovers; in the process, getting antibodies against that virus, which may remain active for variable period time, which may depend on various factors. In those persons, in whom the activity of Innate Immunity has lowered to a great extent, the virus has decisive advantage because it grows faster than what the weak Innate Immunity can counter it, and by the time the Adaptive Immunity gets time to develop anti-bodies, it is too much late.

Thus, it is clear, while sanitation and social distancing are important to control a pandemic, these measures have practical limitations on the side of compliance by general public; and the Innate Immunity compromised persons in the population keep the chain of infection growing and un-controlled.

It is very much clear that improvement in Innate Immunity of Innate Immunity compromised persons is the only key and the most appropriate key to achieve break in the chain of infections in a situation when social distancing compliance by the population is impossible to control.

This key shall be most easy to use when there is no community transmission, since it is easy to identify hot-spots and containment areas, and concentrate on improvement of Innate Immunity of ALL Immune Compromised persons.

Besides this, improvement in Innate Immunity is useful for even areas in which there is no

coronavirus infection in that locality.

Ideally, every person should, as a matter of precaution, look for means for ensuring that Innate Immunity is kept at optimum status.

Unique Importance of β -carotene for Innate immunity compromised people: In elderly, Innate Immunity is compromised, but it is restored by β -carotene supplementation (Hughes,1999, Santos et al, 1996).

Synthetic β -carotene is available. However, clinical trial evidence shows that Bioavailability of beta carotene was better when, instead of isolated crystalline beta carotene, the same was provided through a mixed fruit and vegetable dehydrated juice Samman et al (2003). Ben-Amotz and Levy (1996) wrote that the differences between natural and synthetic beta-carotene "should provoke a shift in scientific attention to natural sources of carotenoids and their role in cancer prevention.

A randomized crossover study has provided evidence that Purple Sweet Potato leaves 200g per day for 20 days increased proliferation responsiveness of PBMC, secretion of cytokines IL-2 and IL-4, **and the lytic activity of Natural Killer Cells** (Chen et al, 2005)., This is a clinical evidence on that the intake of β -carotene provided by Chen et al. through natural source did activate Natural Killer Cells; and this can be used as starting point for clinical nutrition products that would improve Natural Killer Cells. Amongst green leafy vegetables, Purple Sweet Potato leaves contain one of the highest content of β -carotene, almost 6 times higher than in general green leafy vegetables. In view of the fact that Agte et al (2006) recommendation that **"Using 100 g GLV/day with 10 g oil could be a single moderate strategy for supplementation of iron, beta-carotene, ascorbic acid and zinc"**, it is most likely that the result achieved by Chen et al. could have been achieved by at least 6 times lesser intake of β -carotene. However, to be conservative, the content of β -carotene administered by Chen et al. shall be taken as a starting point for making clinical nutrition products for improving activity of Natural Killer Cells; and as experience is gained, the quantity can be brought to a lesser optimum point.

35g Sweet Potato leaves contain 776 μ g β -Carotene
([https://www.healthbenefitstimes.com/health-benefits-of-sweet-potato-leaves/.](https://www.healthbenefitstimes.com/health-benefits-of-sweet-potato-leaves/))

Bioavailability of beta carotene, in terms of beta carotene consumed through food sources to its conversion to Vitamin A is affected by food matrix. When beta carotene is sourced in diet from

Green Leafy Vegetables, this conversion factor by weight, in three cases is 26:1, 27:1 and 28:1 (Tang Guangwen, 2010).

To be conservative, for Sweet Potato Leaves, the factor is considered by us to be 28:1. This means, when 28mg of beta carotene is fed, one mg of Vitamin A is seen in serum arising from this feeding. Since one molecule of beta carotene makes two molecules of vitamin A, that molecule has to be the one that is bio-absorbed from the beta carotene fed through the green leafy vegetable. Hence, for bio-absorption of one molecule of beta carotene, 56 molecules of beta carotene should be fed through green leafy vegetable. Hence, in terms of bio-absorbable beta carotene the ratio is 56:1 by weight.

Chen et al. (2005) has mentioned that daily consumption of treatment group was 23.42 mg β Carotene. At bioavailable beta carotene being 56:1 by weight, the treatment group consumed $(23.42 \times 1000)/56 = 418 \mu\text{g}$ bioavailable β Carotene per day.

Thus, here too, there are reports of lower β Carotene content in Purple Sweet Potato leaves than stipulated by Chen et al. However, to be conservative, to start with, based on clinical trial of Chen et al. (2005), consumption for a human being of 418 μg of bioavailable β -Carotene is taken as a standard that shall modulate various immune functions including increased proliferation responsiveness of PBMC (peripheral blood mononuclear cell), secretion of cytokines IL-2 and IL-4, and the lytic activity of NK cells within a span of two weeks. The lytic activity of NK cells modulated Innate Immunity: the immunity which shall lyse a cell infected by ANY virus, known as well as novel; and 2019 Novel Coronavirus is also a virus, wherein there is no reason that it shall be excluded from efficacy of the Natural Killer Cells to kill cells infected by the 2019 Novel Coronavirus.

Since the active ingredient is β -Carotene, the β -Carotene sourced from any food source would give the effect of modulating Innate Immunity.

According to a clinical trial, β -carotene is absorbable only when it is transferred to fat phase of the meal (Tyssandier 2003). This reference establishes that β -carotene dissolved in fat is bio-absorbable/bio-available. Any other form of β -carotene is poorly bio-absorbable. Hence, we decided to make an oil extract of food source that has reasonably good content of β -carotene, so that whatever is the content by chemical analysis in the oil extract, that much shall be 100% bio-available/bio-absorbable.

Oil extract made from Tomato, named as LeImmune-T, contains at least 418µg β-carotene and, hence, would qualify as an Innate Immunity Booster for Innate Immunity Compromised people.

NK cells have been shown to possess traits of adaptive immunity also (O'Sullivan 2015^a O'Sullivan 2015^b).

Hence, LeImmune-T, which contains at least 418 µg of 100% Bioavailable β-Carotene in a daily dose as provided in label provide improvement in lytic activity of Natural Killer Cells for host cells infected with any pathogenic bacteria and viruses before the pathogens multiply and spread inside the body; and also destroy early stage cancer cells. Novel Coronavirus (SARS-CoV-2) is a virus.

A note on a detailed discussion on above content as well as details of supporting scientific references is attached herewith in the Annexure entitled "Support for label claims" on LeImmune-T attached herewith.

There are several references which are elaborated at the end of above mentioned annexure; some of the references being from reputed and authentic sources and scientific journals such as USDA, American Institute for cancer Research, Int J Cancer., Eur J Nutr, Br J Nutr., Am J Clin Nutr., j.immuni., Innate Immun, U.S. F.D.A., Proceedings of the Nutrition Society, Expert Opinion on Biological Therapy, Advances in Immunology, Journal of Nutrition, American Society for Nutritional Sciences, Cancer Causes Control. Int J Cancer, Eur J Nutr., Journal of Epidemiology, World J Gastroenterol, Asia Pac J Clin Nutr and Am J Physiol Gastrointest Liver Physiol.

Difference between "Innate Immunity Booster" and "Immunity Booster":

It is necessary to avoid identification of "Innate Immunity Booster" as one of the large list of products which are described as "Immunity Booster"/s.

"Immunity Boosters" are those products which have ingredients like zinc, Selenium, Amla etc. that improve activity of cells that mediate "Adaptive Immunity" i.e. an immunity that develops after exposure to a vaccine or to the disease itself and the person recovers from the disease. Thus, if you are looking for protection from Novel Coronavirus infection, unless you have already developed antibodies for the Novel Coronavirus either by getting vaccinated by the vaccine for Coronavirus that is yet to come or you have got infected with the Novel Coronavirus already and either you have not developed infection because of your already strong Innate

Immunity or have developed the disease and have recovered from it, such “Immune Boosters” are not relevant.

Above established science confirms that, substantial scientific evidence exists so far for only one ingredient that improves Natural Killer Cells activity, thereby improving Innate Immunity: and that is β -carotene; sourced from any food source that contains reasonable quantity of β -carotene, and its effective amount is, at today’s available clinical evidence, at least 418 μg of bioavailable β -carotene in one day dose.

In other words, a product is eligible to be called as an “Innate Immunity Booster” only if it contain 418 μg bioavailable β -carotene in one day’s dose. It is only an “Innate Immunity Booster” that shall improve activity of the “Natural Killer Cells” and only “Natural Killer Cells” have an ability to detect a virus infected cell or an early stage cancerous cell as “non-self” and destroy it in first few hours of invasion/formation in body so that the virus or the cancer cell do/es not get opportunity to multiply and set on the disease.

LeImmune-T: the only products that have capability to bring early and conclusive end to Cobid-19 Pandemic: Thus, Innate Immunity Booster nips out the problem in the bud itself; and in the fight against Novel Coronavirus, if Innate Immunity Booster is given **to ALL immune-compromised persons, it will not only improve/restore activity of their Natural Killer Cells/Innate Immunity against any virus**; but also help in breaking the chain of infection because it is only the innate- compromised people that have high risk of falling prey to the infection; and if they also again become immune due to improvement in their Innate Immunity to original optimum level, the chain will get broken very easily; this cannot be done by social distancing, hand washing, face masks etc. as stand-alone measures because many people do not comply with them or use them properly or sometimes absolutely endangering themselves as well as others by showing no regard to social distancing, thereby continuing the chain of infection unabated and in ever- increasing speed.

LeImmune-T: for stability of economy of commercial establishments and the Country: Withdrawal of lock-down in a situation when fresh cases are still popping up, and/or every day the number of infected people is increasing, is putting immune-compromised people at far greater risk than the first day of start of lock-down. WHO is giving warning that withdrawal of lock-down is not end of pandemic when infections are still spreading.

Hence, particularly for offices and industrial establishments having large number of employees,

if after re-start of work after lockdown is withdrawn is to be protected from potential re-imposition of repeat lock-down, ideal way is to ensure that every individual in the society consumes LeImmune-T. However, in practical circumstances, until this product becomes available to each and everybody, prioritization may be needed to be made. First priority should be to persons with highest risk of infection and their family members, which includes is to doctors, nurses, ward-boys, sanitation employees of Covid-Hospital, policemen working in high risk areas, persons serving in cremation of dead bodies and all professionals whose profession is connected to high infection risk areas and Innate Immunity-compromised persons (Type-II diabetics, hypertensives, heart diseased, cancer patients, Chronic-Kidney-Disease patients of all ages; and elderly persons of 50 years age and above). Next in list should be those who are engaged in high physical strain duties and duties in shifts in factories and their family members. Thereafter should follow all remaining population.

In industrial areas, all industries need to be covered under access to LeImmune so that there is reduction in risk of entire Industrial area getting closed down once again if number of cases increase with withdrawal of lock-down. It is a matter of fact that current surge in number of cases in India is attributed to the limited relaxation provided at the beginning of fourth phase of lock-down. It is now known that relaxations are not cautiously used by a significant number of people. Hence, Innate Immunity improvement route by the Innate Immunity boosters described here may prove to be more practical route for a safer withdrawal.

Restoration of Innate Immunity from its depressed level does take some time, a week or two. Ideally, these Innate Immunity Boosters should be started being provided one or two weeks prior to the relaxation for best effect; so that when the normal working starts, the people whose Immunity is compromised today, shall have their Innate Immunity restored to a great extent.

With protection of innate Immunity compromised employees and Innate Immunity compromised family members of all employees is required to avoid further economic losses. Expenditure on Innate Immunity Booster for these people shall be a far less investment as compared to economic losses, if re-imposition of Lock-down becomes necessary. Additionally, it will help breaking chain of infection, development of "Herd Immunity" in a very safe way; and eradication of Novel Coronavirus; with or without the vaccine.

It is also not certain that the Novel Coronavirus may not mutate. It is also coming to light that the novel Coronavirus emerged in Italy in December, 2019 and this, China claims, is different than pandemic that emerged in China. It would be safer to factor in for a possibility of more than one

strain being in circulation. Further, if it does mutate in future and if new strain/s is/are more virulent and the currently in-process vaccines do not work against them, the currently in-process vaccines or Adaptive immunity developed against them may have to be supplemented with an Innate Immunity Booster, so that the mutated Coronavirus strain/s circulating in the population will also get covered in this dual approach.

WHO has repeatedly stressed that very little is known about this Novel Coronavirus; and it has come to stay for a long time; and worst is yet to come. LeImmune-T shall provide a pro-active and strong support to any action against such a possibility.

Hence, whereas vaccine has necessarily to be developed, it is a time tested method of controlling a pandemic, however, as a matter of abundant precaution, there is safety only if they are considered in combination with defense provided by daily consumption Innate Immunity Boosters described here: LeImmune-T developed from tomato, or any other variation of LeImmune developed on same principles from any other source of bioavailable β -carotene.

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