

May the golden-eyed Savitar come hither!

Shining forth he rises from the lap of the dawn!

Praised by singers, my God Savitar!

Stepped forth and never missed his place!

He steps forth the splendor of the sky the wide!

Secing, far-shining, the shining wanderer!

- Rig Veda, vii, 65

He alone shines!

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All luminaries get illuminated by His Illumination The whole Universe is enlightened by His light!

Health and Nutrition

- Kathopanisad

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Issue 245

Chief Editor: ্রেন্থ্র ইন্সিক্রন্তক ঠাঠারেল। डॉक्टर श्रीनिवासराव वेषचेद्। Dr. Seenivasara's Vepachedu

CONTENTS

COUNTERFEIT MEDICINES - CODE RED NOW TO RACE NOVEL FOOD TO CURB CATASTROPHE - CODE RED TO RACE OPIOID EPIDEMIC MADE IN AMERICA BY US (OEMAUS) TURMERIC

Issue 245

5119 కలి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era స్వస్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेवितम्बी नाम संवत्सर/<u>Swasti Sri Hevilambi Year</u>

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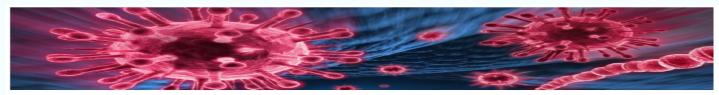
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Issue 245

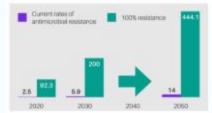
Chief Editor: డాక్టర్ శ్రీనివాసరావు పేపచేదు। डॉक्टर श्रीनिवासराव् वेषचेद्। Dr. Seenivasara's Vepachedu



COUNTERFEIT MEDICINES - CODE RED NOW TO RACE

While patent exclusionary monopoly encourages the innovation, trademarks protect products and services

Global Working-Age Population Lost to Drug-Resistant "Superbugs," In Millions



from the fake and counterfeits of generics, biosimilars, and branded pharmaceuticals available through the Internet, not only on rogue online pharmacies but also on social media and commercial platforms, that can cause problems far beyond brand damage and trademark infringement, leading to serious damage for consumers with potential death. WHO estimates that antimicrobial resistance (AMR) could kill 10 million people per year by 2050 [1].

The growth of international free trade and inadequate drug regulation have led to the expansion of trade in

counterfeit drugs worldwide [2].

The counterfeiting of well-known brands and products is a growing, worldwide issue. Using counterfeit electrical products can result in a higher risk of failure or malfunction, potentially leading equipment failure, property damage, or injury [3].

Counterfeit medicines are recognized as contributing to AMR, since they may have the wrong amount of an active ingredient, none at all, or a different one. Reports from the Pharmaceutical Security Institute, the World Health Organization (WHO), and the World Customs Organization indicate that counterfeit medicines are on the rise and cost EU pharmaceutical industry €10.2 billion (US \$12.4 billion) a year in lost sales, according to a European Union



Intellectual Property Office report with an increased use of e-commerce by the counterfeiters coupled with the difficulty of tracing the source of those selling via these platforms. Anticounterfeiting programs include strong intelligence, prevention, and enforcement capabilities aimed at monitoring (online and offline), detecting, and investigating cases of suspected counterfeits, case linking, and tracing the source of counterfeit products, coupled with a strong enforcement capability working in partnership with

Issue 245

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government enforcement agencies in multiple jurisdictions to close down counterfeit operations, and working with consumers because the consumer demand outside the legitimate supply chain creates an ideal environment for counterfeiters [4].

Since the manufacture of penicillin during World War II, antimicrobial drugs have been the source of wellness to many who have suffered life-threatening infections. Over the last 70 years, however, we have taken these drugs for granted and now face the consequences of AMR [5]. Growing numbers of bacterial and viral infections are resistant to antimicrobial drugs, but no new classes of antibiotics have come on the market for more than 25 years [6].

In Europe, drug-resistant bacteria are responsible for 25,000 deaths a year, with related healthcare costs and productivity losses of €1.5 billion (\$2 billion); over half a million people worldwide have drug-resistant tuberculosis; in US, about 15 % of pneumococcal isolates are resistant to penicillin [7]. Each year in US, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Efforts to prevent antibiotic resistance build on the foundation of proven public health strategies [8].

Dangerous multiple drug-resistant versions of bacteria with human health implications have been detected in Indian major carp or Rohu, a popular aquaculture fish consumed across India. In an examination carried out by the National Institute of Biotic Stress Management of the Indian Council of Agricultural Research in Raipur, Chhattisgarh, the scientists found that Rohu fish were carrying a pathogen associated with hospital-acquired infections. The isolate *Raoultella ornithinolytica* was highly resistant to ampicillin, amoxicillin, clavulanic acid, tetracycline, doxycycline, co-trimoxazole, rifampicin, kanamycin, trimethoprim, oxytetracycline, colistin, and pefloxacin. Raoultella ornithinolytica is a gram-negative encapsulated aerobic bacillus belonging to family Enterobacteriaceae that is found in aquatic environments, fish, and insects. Raoultella ornithinolytica known to transmit antibiotic resistance genes in the food chain and environment, the emergence of this pathogen may potentially cause the public health hazard across the flattened globe of the globalized economy [9]. In India, antibiotic-resistant neonatal infections claim the lives of 60,000 newborn babies each year, according to the Review on Antimicrobial Resistance paper published in 2016. The threat of drug-resistant superbugs has prompted the authorities to issue public awareness messages on state-run radio channels cautioning patients against taking antibiotics without a prescription. Many hospitals have also taken part in a program to control infections. Drug authorities issued a warning to pharmacies against the sale of antibiotics without a prescription. An American woman who had traveled to India died of a rare superbug, recently [10].

More global citizens are able to access and purchase antibiotics, but without effective monitoring by health officials - from doctors to hospital workers to clinicians. India has emerged as the world's largest

Issue 245

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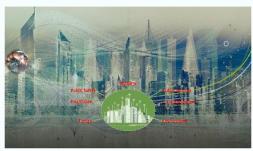
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Issue 245

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consumer of antibiotics, followed by China and US, and India is in the eye of the storm. From the current 7,00,000 deaths per year, superbugs are estimated to kill 10 million people per year globally by 2050. To put the figures in context there are currently 8.2 million deaths a year from cancer and annual global GDP stands at \$70 trillion to \$75 tn, with the UK figure around \$3 tn. India is one of the countries caught in the eye of the storm that will soon hit the entire planet. Of the 10 million deaths worldwide, 2 million are expected to be in India [11].

According to a United Nations report dated 10 July 2014 [12], 54% of the world's population lived in urban areas, and it was expected to increase to 66% by 2050. Projections show that urbanization



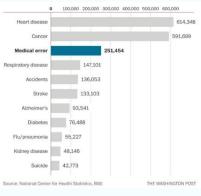
combined with the overall growth of the world's population could add another 2.5 billion people to urban populations by 2050. In 1990, there were ten megacities each with 10 million inhabitants or more, the number of which increased to 28 megacities worldwide in 2014, out of these megacities, sixteen are located in Asia, four in Latin America, three each in Africa and Europe, and two in Northern America. Nearly half of the world's 3.9 billion urban dwellers reside in relatively small settlements with fewer than 500,000 inhabitants, while only around one in eight live in

the 28 megacities with 10 million inhabitants or more. Many of the fastest growing cities in the world are

relatively small urban settlements. Tokyo remains the world's largest city with 38 million inhabitants; followed by Delhi with 25 million; Shanghai with 23 million; Mexico City, Mumbai and São Paulo, each with around 21 million; Osaka with over 20 million; Beijing with about 20 million; and the



New York-Newark area and Cairo with around 18.5 million inhabitants each. UN press release of revised statistics on 16 May 2018 stated that out of the total world population, 55% lived in urban areas in 2018 which is projected to increase to 68% by 2050, and by 2030,



the world is projected to have 43 megacities with more than 10 million inhabitants. As the world continues to urbanize, sustainable development depends increasingly on the successful management of urban growth, as many countries will need integrated policies to improve the lives of both urban and rural dwellers, facing challenges in meeting the needs of the growing urban populations for housing,

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transportation, energy systems and other infrastructure, for employment and basic services such as education and healthcare, and to ensure that the benefits of urbanization are fully shared and inclusive with access to infrastructure and social services for all in a safe environment [13], we need smart cities

[14] with Novel Food To Curb Catastrophe [15].

And the all which which we can experience with the all control and the all control and

Although we might think we are isolated by oceans from the rest of the world, the earth is a biosphere without barriers. Human-made border lines, oceans, and walls constructed around US are just our imaginary lines, and fail to prevent the diffusion through the atmosphere and water. Smallpox, syphilis, plague, cholera – some of the planet's most notorious scourges dramatically expanded their reach thanks to unsuspecting travelers. New disease-causing microbes have never traversed the planet faster.

It is Code Red now to RACE (Remove, Alert, Contain & Evacuate). Curbing this ongoing catastrophe should thus be of high concern for

people aiming to effectively help as many sentient beings as possible with Novel Food To Curb Catastrophe [15].

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Issue 245

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Issue 245

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NOVEL FOOD TO CURB CATASTROPHE - CODE RED TO RACE



"Addressing this massive challenge would ideally involve a worldwide shift to a vegetarian lifestyle, but such a shift is unlikely to take place in our lifetimes. Curbing this ongoing moral catastrophe should thus be of high concern for all people."



Non-human sentience: There is scientific consensus regarding animal sentience and their capacity to suffer 42 and this is officially recognized in EU legislation 43. The opposing view that conscious experience is only possible in human brains is not supported by current evidence 44,45. It follows that any needless suffering inflicted upon animals under human care, whether through direct action or inaction/neglect, is morally indefensible and must be stopped.

"The absence of a neocortex does not appear to preclude an organism from experiencing affective states. Convergent evidence indicates that non-human animals have the neuroanatomical, neurochemical, and neurophysiological substrates of conscious states along with the capacity to exhibit intentional behaviors. Consequently, the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Nonhuman animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates." The Cambridge Declaration on Consciousness, The University of Cambridge, 7 July 2012

There is a scientific consensus regarding animal sentience and their capacity to suffer and this is officially recognized in EU legislation [1]. The opposing view that conscious experience is only possible in human brains is not supported by current evidence [2]. It follows that any needless suffering inflicted upon animals under human care, whether through direct action or inaction/neglect, is morally indefensible and must be stopped [3].

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era స్వస్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवत्सर/<u>Swasti</u> <u>Sri Hevilambi Year</u>

జ్యేష్ట్ర మాసము/JYESHTA Month Published online 1 JUNE 2018

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<u>Home</u>	<u>The Foundation</u>	<u>Management</u>	<u>The Andhra Journal of Industrial News</u>	The Telangana Science Journal	<u> Mana Sanskriti (Our Culture)</u>
<u>Vegetarian Links</u>	<u>Disclaimer</u>	Solicitation	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

Chief Editor: chief Editor: ্রেন্থ্র ইন্সিক্রমত হা ইন্রের্ম। डॉक्टर श्रीनिवासराव वेपचेद्। Dr. Seenivasara's Vepachedu

The main causes of climate change are usually attributed to transportation and housing, ignoring another and most significant contributor, according to the UN Food and Agriculture Organization (FAO), animal agriculture that is responsible for about 14.5% or more of the world's total Greenhouse Gas (GHG) emissions. Therefore, it is as bad for the environment as the combined impact of every motor vehicle in the world, collectively contributing about the same GHG emissions, 15%. Methane, whose global warming potential is times greater than that of carbon dioxide, makes up 44% of the animal industry's total emissions. Most of this methane is emitted by ruminants such as cows, sheep, and goats as a natural by-product of their digestive processes.

The United Nations Environment Program (UNEP) maintains that a reduction of greenhouse gas emissions of at least 50% by 2050 is necessary in order to avoid the worst impacts of climate change.



Industrial livestock production presents a growing problem on a global scale in terms of animal welfare, environmental sustainability, and human health. Each year, more than 60 billion sentient animals are reared in industrial conditions in order to produce meat. This global enterprise is currently the planet's main source of human pandemic diseases and likely among its greatest concentrations of human-inflicted suffering. Curbing this ongoing moral catastrophe should thus be of high concern for people aiming to effectively help as many sentient beings as possible.

Dangerous multiple drug-resistant versions of bacteria with human health implications have been detected in Indian major carp or Rohu, a popular aquaculture fish consumed across India, one of the countries caught in the eye of the storm that will soon hit the entire planet. Of the 10 million deaths due to Antibiotic and Multi-Drug Resistance, 2 million are expected to be in India. Although we

might think we are isolated by oceans from the rest of the world, the earth is a biosphere without barriers. Human-made border lines, oceans, and walls constructed around US are just our imaginary lines, and fail to prevent the diffusion through the atmosphere and water. It is Code Red now to RACE (Remove, Alert, Contain & Evacuate) (see It is Code Red to RACE).

Moreover, the fact that "animal agriculture contributes to climate change and makes inefficient use of a significant portion of our available resources," remains a verifiable scientific fact whether anyone in US agrees with it or not, or believes it to be fake to protect the vested interests of the Corporate Capitalism of US, interested in a different kind of harvest - The Opioid Epidemic Made in America by US (OEMAUS)

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్లమార్క కాలము/Vikramarka Era| 1939 శారివాహన కాలము/Salivahana Era స్పప్తి శ్రీ విళంచి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवत्सर/<u>Swasti Sri Hevilambi Year</u>



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<u>Home</u>	The Foundation	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	Mana Sanskriti (Our Culture)
<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

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Recycling to Create Jobs with Matching Organs Saving Lives, and Create Orphans To Make America Great Again!

Addressing this massive challenge would ideally involve a worldwide shift to a vegetarian lifestyle, but such a shift is unlikely to take place in our lifetimes. Humans around the world place a high value on meat in terms of taste, nutrition, affluence, culture, and tradition, evidenced in part by a clear rise in global meat consumption over the past half-century — a trend strongly associated with economic growth in newly industrializing countries in the East and West.

Despite the vegetarian movement witnessed steady growth in recent years in the West, its growth pales in comparison to the global demand and craze for meat rising from the East (e.g., endangering the Donkey) and West, which is predicted to increase by 73% within 2050. Meanwhile, plant-based meat substitutes have, despite decades of costly improvements, not proven sufficiently effective at replacing and curbing the meat addiction that is culturally and religiously ingrained in people's diets, e.g., See Downtrodden Golla Christian Professor Kanche Iliaha's anti-Brahmin, anti-Hindu, and anti-Semitic, "Why I am Not a Hindu." In view of such entrenched and bigoted views and attitudes in the East towards Mahatma Gandhi's vegetarian humane approach toward food, combined with the Western cultural view of diet influencing the entire world through Hollywood and Globalization, it would thus be a significant gain if we were able to introduce a cruelty-free replacement for meat with the ability to rival conventional livestock-production [4].

One solution might be cultured meat, in which animal tissue is grown in a controlled environment using cell culture technology, thereby making the raising and killing of animals for food unnecessary. This approach shows a great potential for meeting all the requirements of a humane, sustainable and healthy form of meat production. By gradually replacing animal agriculture, large-scale production of cultured meat could greatly reduce animal suffering, human disease risk, and environmental problems [5].

Cultured Meat Manufacturing (CMM) process starts with cells taken from livestock or poultry, which are then coaxed to grow into strands of muscle, in bioreactors shown here on the left [6]. The CMM technology would spare animals from slaughter, require less energy and land, and emit fewer greenhouse gases than conventional meat production does. The world watched the first lab-grown small pink beef patty out of a petri dish and fried in front of the media, the proof that it was possible to grow safe and edible meat without slaughtering a single animal, 5 years ago. The patty had taken two years and over \$300,000 to produce. But since then the cost of producing this high-tech meat has plummeted. In January 2016, a company called Memphis Meats produced a 'cultured meatball' for around \$1,000, and today start-ups and non-profit organizations are working on other lab-grown animal products including pork chicken, turkey, fish, milk, egg whites, gelatin, and even leather [7].

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్షమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era సస్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवत्सर/S<u>wasti Sri Hevilambi Year</u>



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<u>Home</u>	The Foundation	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	Mana Sanskriti (Our Culture)
<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

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In 2012, the environmental impacts of the hypothetical large-scale production of cultured meat were compared to the impacts of livestock production in the EU-27. The results showed that if all meat produced in the EU-27 was replaced by cultured meat, the GHG emissions, land use and water use would be reduced by two orders of magnitude compared to current meat production practices. When the opportunity costs of land use were included, the environmental benefits were even higher [8].

The US Department of Agriculture (USDA) is responsible for ensuring the quality of meat, poultry, and egg products. The US Food and Drug Administration (USFDA) is responsible for the safety of therapies made from cells and tissues, processed foods, seafood, and genetically engineered animals. The US House of Representatives added language to a draft spending bill that would put USDA in charge of overseeing the manufacturing and labeling of cultured meat grown from cells in bioreactors [9].

The European Union is way ahead of US, without the so-called Corporations that are people with first amendment rights under the Constitution to influence/ lobby/ bribe/ brainwash the People and Government - Congress, Executive, and Judiciary of US! As a result, the emergence of EU as a superpower having friendly relations with Russia is a grave threat to the American Way of Life as the Beacon of Hope of Shining Democracy on the Capitalist Hill.

Nevertheless, in the EU, rules that went into effect in January declared cultured meat to be a category of Novel Food that can be marketed there if regulators decide it is safe, nutritionally equivalent to a food it is intended to replace and labeled so as not to mislead consumers.

Novel Food is defined as food that had not been consumed to a significant degree by humans in the EU before 15 May 1997, when the first Regulation on novel food came into force. Novel Food can be newly developed, innovative food, food produced using new technologies and production processes, as well as food which is or has been traditionally eaten outside of the EU. Examples of Novel Food include new sources of vitamins, extracts from existing food, agricultural products from third countries, or food derived from new production processes [10].

As of 1 January 2018, the new Regulation (EU) 2015/2283 on novel foods (the new Regulation) is applicable. It repeals and replaces Regulation (EC) No 258/97 and Regulation (EC) No 1852/2001 which were in force until 31 December 2017 [11].

Issue 245



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<u>Home</u>	The Foundation	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	Mana Sanskriti (Our Culture)
<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

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Animal Consciousness Officially Recognized by Leading Panel of Neuroscientists

Cambridge Declaration on Consciousness: A step in the right direction

Animals are sentient and conscious

Scientists Give Animals Consciousness

PIGS USE MIRRORS TO FIND HIDDEN FOOD

Dolphin cognitive abilities raise ethical questions, says Emory neuroscientist

Molecular Contiguity between Human and Animal Consciousness through Evolution: Some Considerations

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Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era స్వప్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेविनम्बी नाम संवत्सर/<u>Swasti Sri Hevilambi Year</u>

జ్యేష్ణ మాసము/JYESHTA Month Published online 1 JUNE 2018



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<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

Chief Editor: డాక్టర్ శ్రీనివాసరావు పేపచేదు। डॉक्टर श्रीनिवासरावु वेषचेदु। Dr. Sneenivasana's Vepackedu

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As of 1 January 2018, the new Regulation (EU) 2015/2283 on novel foods (the new Regulation) is applicable. It repeals and replaces Regulation (EC) No 258/97 and Regulation (EC) No 1852/2001 which were in force until 31 December 2017.

The new Regulation improves conditions so that food businesses can easily bring new and innovative foods to the EU market, while maintaining a high level of food safety for European consumers.

The main features and improvements of the new Regulation are the following:

- Expanded categories of Novel Foods: The Novel Food definition describes the various situations of foods originating from plants, animals, microorganisms, cell cultures, minerals, etc., specific categories of foods (insects, vitamins, minerals, food supplements, etc.), foods resulting from production processes and practices, and state of the art technologies (e.g. intentionally modified or new molecular structure, nanomaterials), which were not produced or used before 1997 and thus may be considered to be as novel foods.
- Generic authorizations of Novel Foods: Under the new Regulation, all authorizations (new and old) are generic as opposed to the applicant-specific, restricted novel food authorizations under the old Novel Food regime. This means that any food business operator

Issue 245

5119 sවి కాలము/Kali Era| 2075 విక్లమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era స్వప్తి శ్రీ విళంబి నామ సంపత్సరము/स्वस्ति श्री हेविलम्बी नाम संवत्सर/<u>Swasti Sri Hevilambi Year</u>



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<u>Home</u>	<u>The Foundation</u>	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	Mana Sanskriti (Our Culture)
<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

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can place an authorized Novel Food on the European Union market, provided the authorized conditions of use, labeling requirements, and specifications are respected.

- Establishment of a Union list of authorized Novel Foods: This is a positive list containing all authorized novel foods. Novel Foods which will be authorized in the future will be added to the Union list by means of Commission Implementing Regulations. Once a novel food is added to the Union list, then it is automatically considered as being authorized and it can be placed in the European Union market.
- A simplified, centralized authorization procedure managed by the European Commission using an online application submission system.
- Centralized, safety evaluation of the Novel Foods will be carried out by the European Food Safety Authority (EFSA). The European Commission consults EFSA on the applications and bases its authorization decisions on the outcome of the EFSA's evaluation.
- Efficiency and transparency will be improved by establishing deadlines for the safety evaluation and authorization procedure, thus reducing the overall time spent on approvals.
- A faster and structured notification system for traditional foods from third countries on the basis of a history of safe food use. To facilitate the marketing of traditional foods from countries outside the EU, which are considered novel foods in the EU, the new Regulation introduces a simplified assessment procedure for foods new to the EU. If the safety of the traditional food in question can be established on the basis of evidence of a history of consumption in the third country, and there are no safety concerns raised by EU Member States or EFSA, the traditional food will be allowed to be placed on the European Union market.
- Promotion of innovation by granting an individual authorization for five years based on protected data. Data protection provisions are included in the new Regulation. That means that an applicant may be granted an individual authorization for placing on the market of a novel food. This is based on newly developed scientific evidence and proprietary data and is limited in time to 5 years.

Issue 245



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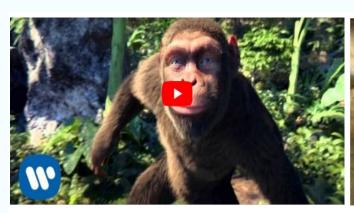
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HomeThe FoundationManagementThe Andhra Journal of Industrial NewsThe Telangana Science JournalMana Sanskriti (Our Culture)Vegetarian LinksDisclaimerSolicitationContactVPCVedah-net

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The Foundation Management The Andhra Journal of Industrial News The Telangana Science Journal Mana Sanskriti (Our Culture) Home <u>Vegetarian</u> Links Vedah-net Disclaimer **Solicitation VPC Contact**

Issue 245

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OPIOID EPIDEMIC MADE IN AMERICA BY US (OEMAUS)



Organs Harvested In Self Inflicted American Opioid Epidemic By US Opioid Harvest of Matching Organs Saves Lives and Creates Jobs Organs From Drug-overdose Deaths Are Suitable For Transplantation The Opioid Epidemic Has Boosted the Number of Organs Available for Transplant

About 114,905 people across the country are on organ transplant waiting lists in US. If you don't believe

in the environmental benefits of recycling based on fake science, think of the employment that it can generate and American lives it can save among US.

Thanks to the opium availability through the war machine, US has created an opportunity, hitherto unavailable, to use the body parts of the victims of the Opioid Epidemic Made in America by US (OEMAUS).

According to research published by Brigham and Women's Hospital, the organs of victims of good the **OEMAUS** are for organ transplantations. US is already in the business of harvesting organs from the opioid victims



and there has been a 17.4-fold increase in the proportion of donors who died from drug intoxication between the year 2000 (59, when opium was banned in Afghanistan and 99% of the opium crop was destroyed with a devastating blow to the opium supply to OEMAUS victims among US) and 2016 (1,029, 17.4-fold since the restoration of opium supply for US after the opium production was restored after US invasion of Afghanistan in search of Saudi Arab citizen Osama bin-Laden living in Abbottabad, Pakistan). US is hopeful that doctors across the country will read this and feel confident that organs that pass the required tests are safe for the transplant because donors died from Opioid Epidemic Made in America by US and this awareness is especially important when organ procurement professionals harvest the OEMAUS Donors' Body Parts.

US should encourage every alien and native American to sign up to be an organ, eye and tissue donor, especially those who are addicted to opioid pharmaceuticals (e.g., fentanyl), opium derivatives (e.g.,

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శాలివాహన కాలము/Salivahana Era స్వప్తి శ్రీ విళంచి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवत्सर/<u>Swasti</u> <u>Sri Hevilambi Year</u>

జ్యేష్ట్ర మాసము/JYESHTA Month Published online 1 JUNE 2018



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-Rio Veda, vii, 65

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HomeThe FoundationManagementThe Andhra Journal of Industrial NewsThe Telangana Science JournalMana Sanskriti (Our Culture)Vegetarian LinksDisclaimerSolicitationContactVPCVedah-net

Issue 245

Chief Editor: ্রেন্থ্র ইন্সিক্রন্তক ঠাঠারেল। डॉक्टर श्रीनिवासराव वेषचेद्। Dr. Seenivasara's Vepachedu

heroin), and cocaine, whose body parts are useful and will be available soon for harvesting and reuse at Matching Organs Saving Lives https://Unos.Org/Donation/Register-To-Be-An-Organ-Donor/.

According to a study published in the New England Journal of Medicine (June 2017), even such modest reductions in pollution could save more than 10,000 lives of Americans per year in US. A study published in JAMA (December 2017) linked pollution level to premature death among the elderly. According to SCIENCE (4 MAY 2018), lowering the standard from 15 micrograms per cubic meter air to 11 micrograms per cubic meter air would save about \$ 20 billion and cost \$ 1.3 billion, with a net gain of \$ 18.7 billion.

With the aid of a warming planet and modern means of transportation, mosquitoes that carry chikungunya and related viruses are spreading. Once limited to Asia and Africa, chikungunya (pronounced chick-un-GOON-ya) virus has infected more than a million people in the Caribbean and South America in an outbreak that began in 2013 and continues to this day. There are no specific treatments or vaccines for chikungunya and related viruses, known as arthritogenic alphaviruses, because there was no need for US to develop such medications for such diseases that infest the *hithole countries, until now. Finally, thanks to the non-existent fake climate change chikungunya virus is a growing threat to US as the alien mosquito that carries the virus expands its reach immune Trump's ban on criminal aliens and to Pruitt/Putin's chlorpyrifos/novichok/VX.

Chikungunya infection produces symptoms of fever and joint pain resulting in a debilitating and painful form of arthritis. US travelers have brought it home to more than half the states in US. Like it or not, the alien criminal is here among US and its name chikungunya comes from the alien Makonde language of an alien *hithole country Tanzania meaning which bends up or to walk bent over suffering from painful arthritis, where it was first identified in the early 1950s. Let us not miss this opportunity to make a buck by concocting a treatment protected by a public franchise monopoly called patent for exclusionary rights to prevent others using the treatment until we make enough money by charging US for our innovation, R&D, marketing, fake news and ads, and multi-million dollar CEOs with private jets.



By the way, "Putin is behind the invasion of US by alien mosquitos infested with arthritogenic alphavirus chikungunya from the *hithole countries," says the Ambassador of US for the United Nations Security Council for the West, "there is enormous evidence including the pictures showing a microscope, mosquitoes, and Petri dishes with virus concoctions which are most probably the

Issue 245

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<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

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arthritogenic alphavirus chikungunya cocktails and that Putin with his expertise in virology created the biological weapon of arthritogenic alphavirus chikungunya," and warned Putin to behave or else Russia will face the music.

REFERENCES AND NOTES

Organs Harvested In America By US

https://unos.org/Donation/Register-To-Be-An-Organ-Donor/

Why Chikungunya, Other Arthritis-Causing Viruses Target Joints PRUITT WILL KILL US Afghanistan's Poppy Fields & US Military

The Centuries-Old Great Game



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Issue 245

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FORMULATION OF TURMERIC

Powdered turmeric root has millennia in the Indian and carminative at dosages of 3 to 6 g/day have been effects against ulcers. Daily 3,600 mg have been trials. but dosages of have been used. Several turmeric/curcumin has



traditionally been used for Continent as a stimulant of 0.5 to 3 g/day. Dosages investigated for protective oral doses of curcumin typically used in clinical curcumin up to 8 g/day recent studies show that anti-inflammatory

properties and modifies immune system responses. A 2006 study showed turmeric was more effective at preventing joint inflammation than reducing joint inflammation.



10 Proven Health Benefits of Turmeric and Curcumin

Turmeric is an old Indian spice with a powerful medicinal compound called Curcumin. Here are the top 10 health benefits of hymnatic/curcumin

A 2010 clinical trial found that a turmeric supplement called Meriva (standardized to 75 percent curcumin combined with phosphatidylcholine) provided long-term improvement in pain and function in 100 patients with knee OA. In a small 2012 pilot study, a curcumin product called BCM-95 reduced joint pain and swelling in patients with active RA better than diclofenac, a nonsteroidal anti-inflammatory drug

(NSAID).

• Over 200 unique compounds have been identified in turmeric including Turmerones: 109 sesquiterpenes, 68 monoterpenes, 22 diarylheptanoids, 8 phenolic compounds, 5 diterpenes, 4 sterols, 3 triterpenes, 2 alkaloids.

EP2555787 (B1) - FORMULATION OF CURCUMIN WITH ENHANCED BIOAVAILABILITY OF CURCUMIN AND METHOD OF PREPARATION AND TREATMENT THEREOF: A composition of a curcuminoid mixture and added essential oil of turmeric, wherein the curcuminoid mixture comprises curcumin, demethoxycurcumin and bisdemethoxycurcumin, and wherein the essential oil of turmeric comprises 45 % (S)-2-Methyl-6-(4-methylphenyl)-2-hepten-4-one ((S)-Ar-turmerone), for use in treatment of depression, wherein the weight ratio of the curcuminoid mixture to the essential oil of turmeric is 10:1 and wherein the composition is administered in a dose of 500 mg twice daily for 8 weeks.

Issue 245

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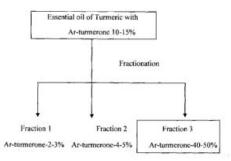
Issue 245

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(54) Title: FORMULATION OF CURCUMIN WITH ENHANCED BIOAVAILABILITY OF CURCUMIN AND METHOD OF PREPARATION AND TREATMENT THEREOF

Fig: 5: Method of preparation of Essential oil of turmeric with varying concentration of

Ar-turmerone.



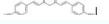
(57) Abstract: A formulation of curcuminoid with essential oil of turmeric to enhance the bioavailability and to augment the biological activity of curcumin is disclosed, wherein curcumin is the main constituent of curcuminoid and Ar-turmerone is the main constituent of the essential oil of turmeric. The use of the formulation in the manufacture of medicament for the treatment of a variety of diseases is also disclosed.

Constituents from turmeric:

Curcumin

Demethoxycurcumin

Bisdemethoxycurcumin



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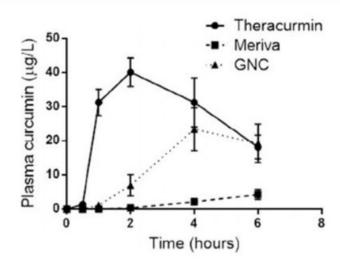
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<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

Chief Editor: a se क्री क्री क्रा कर के क्री क्रिक्ट क्री क्रिक्ट क्री निवासराव् वेषचेद्। Dr. Sneenivasara's Vepachedu

FIGURE 2. Kinetics of curcumin absorption of blood collected at 0.5, 1, 2, 4, and 6 hours after capsule consumption. For the 10 healthy volunteers enrolled in the bioavailability study (see supplementary material), three forms of curcumin were compared. Theracurmin® was absorbed faster (T-max: 2 hours) than GNC Herbal Plus Standardized Turmeric® (4 hours: supplied by GNC [Pittsburgh, PA]) and Meriva® (6 hours; supplied by Indena SpA [Milan, Italy]). Theracurmin consumption also led to significantly higher peak concentrations $(40.1 \pm 13.3 \,\mu\text{g/L})$ and areas under the curve $(165 \pm 64 \,\mu\text{g} \times \text{hour/L})$ compared with GNC Herbal Plus Turmeric (23.4 \pm 18.8 μ g/L, $74 \pm 70 \,\mu\text{g} \times \text{hour/L}$), and Meriva $(4.2 \pm 4.6 \,\mu\text{g/L})$, $9 \pm 8 \,\mu g \times hour/L$).



Curcumin has previously been shown to have anti-inflammatory and antioxidant properties in lab studies. It also has been suggested as a possible reason that senior citizens in India, where curcumin is a dietary staple, have a lower prevalence of Alzheimer's disease and better cognitive performance. The research,

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శారివాహన కాలము/Salivahana Era స్వప్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवतसर/<u>Swasti Sri Hevilambi Year</u>



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Chief Editor: ্রেন্থ্র ইন্সিক্রন্তক ঠাঠারে। डॉक्टर श्रीनिवासराव् वेषचेद्। Dr. Sreenivasara's Vepachedu

published online Jan. 19 in the American Journal of Geriatric Psychiatry, examined the effects of an easily absorbed curcumin supplement on memory performance in people without dementia, as well as curcumin's potential impact on the microscopic plaques and tangles in the brains of people with Alzheimer's

TABLE 3. Baseline and 18-Month Regional FDDNP Binding Levels, Percent Changes, and Effect Sizes

	Curcumin			Placebo			Effect Size		
Regions	Baseline	18-Month	% Change	Baseline	18-Month	% Change	Within Curcumin	Within Placebo	Between Group
Frontal	1.11 (0.05)	1.10 (0.06)	-0.63	1.15 (0.08)	1.13 (0.08)	-1.52	-0.13	-0.22	-0.10
Parietal	1.04 (0.06)	1.06 (0.06)	1.38	1.07 (0.05)	1.07 (0.05)	-0.51	0.24	-0.11	-0.35
Lat Temp	1.11 (0.05)	1.12 (0.05)	0.64	1.13 (0.08)	1.14 (0.07)	0.50	0.14	0.08	-0.06
Med Temp	1.16 (0.06)	1.17 (0.07)	0.52	1.18 (0.07)	1.19 (0.06)	1.31	0.09	0.23	0.14
Post Cingul	1.13 (0.06)	1.12 (0.05)	-0.88	1.14 (0.08)	1.14 (0.06)	-0.17	-0.19	-0.03	0.16
Ant Cingul	1.18 (0.06)	1.18 (0.05)	-0.16	1.22 (0.09)	1.20 (0.08)	-1.50	-0.04	-0.21	-0.17
Amygdala ^a	1.29 (0.06)	1.26 (0.06)	-2.05	1.31 (0.11)	1.32 (0.10)	0.62	-0.41	0.08	0.48
Hypothalamus ^b	1.42 (0.06)	1.40 (0.06)	-1.31	1.42 (0.14)	1.46 (0.13)	2.52	-0.30	0.26	0.55

Notes: Values are provided as mean (standard deviation). Ant Cingul: anterior cingulate; Lat Temp: lateral temporal; Med Temp: medial temporal; Post Cingul: posterior cingulate.

The volunteers underwent positron emission tomography, or PET scans, to determine the levels of amyloid and tau in their brains at the start of the study and after 18 months. ... Previous studies suggested that this time period would be sufficient to detect significant changes in FDDNP-PET binding levels in nondemented middle-aged and older adults (Small et al., Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 8-Month Trial, Am J Geriatr Psychiatry 26:3 (March 2018)).

Trend in between group difference (p = 0.07); significant decrease within the curcumin group (p = 0.04).

 $^{^{}b}$ Significant between group difference (p = 0.02); significant increase within the placebo group (p = 0.05).



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Curcumin metabolites Curcumin Piperine i.v/ i.p H₃CO COO-Tetrahydrocurcumi OH ОН Curcumin glucuronide OH H₃CO OH lexahydrocurcumin Curcumin sulphate OH осн3 Hexahydrocurcumino

Curcumin-loaded solid lipid nanoparticles (C-SLNs) labeled with Technetium-99m (99mTc) radioisotope are a new radiopharmaceutical alternative to 99mTc-labeled compounds that are used in liver and spleen imaging in colloid scintigraphy (Evaluation of radiolabeled curcumin-loaded solid lipid nanoparticles usage as an imaging agent in liver-spleen scintigraphy, Mater Sci Eng C Mater Biol Appl. 75: 663-670 (2017 June 1); An Investigation of the Usability of Solid Lipid Nanoparticles Radiolabelled with Tc-99m as Imaging Agents in Liver-Spleen Scintigraphy, J Biomed Nanotechnol. 12(7): 1501-09 (2016 July)). Fluoropropyl-substituted curcumin [18F] is metabolically stable in the brain and is a suitable radioligand for Aβ plaque imaging (Curcumin and Dehydrozingerone Derivatives: Synthesis, Radiolabeling, and Evaluation for β-Amyloid Plaque Imaging, J. Med. Chem., 49 (20), pp 6111–6119 (2006)).

Curcumin has the potential for targeting lymphomas, which may be used as diagnostic/ therapeutic agent by labeling with radionuclides such as 125-I . Curcumin has been derivatized for its labeling with PET radionuclides such as 18-F for possible use in diagnosis of β -amyloid plaque imaging and tumor.

Clinically, relevant radioactive isotopes of iodine include 123 I (T1/2 = 13.1 h, E γ = 159 keV), which is relevant in diagnostic imaging and 131 I (T1/2 = 8.04 d, E β = 606 keV), which is a therapeutic isotope.125 I (T1/2 = 60.14 d, E γ = 35 keV) with its convenient half-life and emission properties makes it easy to prepare and evaluate radioiodinated derivatives, whose *in vitro* uptake and *in vivo* localization data may

Issue 245

5119 కరి కాలము/Kali Era| 2075 విక్రమార్క కాలము/Vikramarka Era| 1939 శారివాహన కాలము/Salivahana Era స్వప్తి శ్రీ విళంబి నామ సంవత్సరము/स्वस्ति श्री हेविलम्बी नाम संवतसर/<u>Swasti Sri Hevilambi Year</u>

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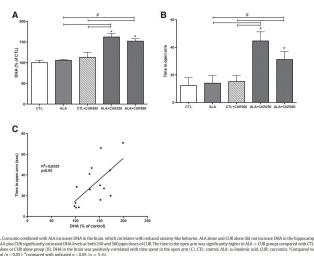
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Vegetarian Links	<u>Disclaimer</u>	Solicitation	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

Chief Editor: డాక్టర్ శ్రీనివాసరావు పేపటేదు। डॉक्टर श्रीनिवासराव् वेषचेद्। Dr. Seenivasara's Vepachedu

provide useful information on the performance of 123 I and 131 I labeled curcumin (Evaluation of radioiodinated curcumin for its potential as a tumor-targeting radiopharmaceutical, J Radiat Cancer Res, 7:4, pp 112-6 (2016); Bioavailability of Curcumin: Problems and Promises, Curcumin: A multi-target disease-modifying agent for late-stage transthyretin amyloidosis https://www.nature.com/articles/srep26623).



Changes in farming practices in the West and food consumption over the last century resulted in the dietary n-3 fatty content decline. For example, aquaculture currently accounts for nearly one-half of the seafood supply for human consumption in the world, which is a large increase compared with the 1980's, where aquaculture contributed only 9% or even in 2000 where fisheries made up 34%. Terrestrial oilseeds and maize are commercially used in fish feed, which can increase the ratio of n-6:n-3 in seafood. Other dietary sources of DHA, such as beef and eggs have reduced DHA content when using the most prevalent

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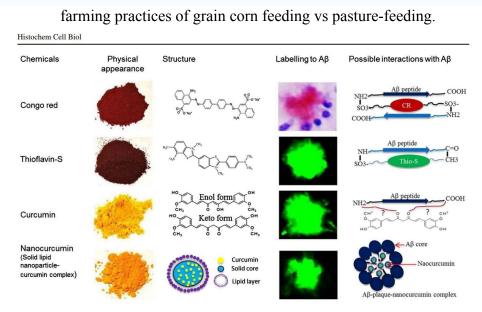


Fig. 1 Comparison of Cur, NC with classical amyloid-binding dyes. Different parameters, including their chemical structure, physical appearance, binding to A\beta, and possible interactions with A\beta were compared with Cur, NC, Thio-S, and CR

Thus, even for omnivores, obtaining DHA through the diet may be increasingly difficult in the current modern food climate. Paradoxically, in the Indian Continent, and particularly in India, where vegetarianism has been practiced for millennia (albeit, the traditional vegetarian population is only about 5% of the entire Indian population and ranging from less than 2% in some states like Telangana, Andhra Pradesh, Tamilnadu, etc., to about 10% in some states like Gujarat), the incidence of cognitive impairment due to low DHA was not observed among those vegetarians. Increasingly, vegetarianism and veganism are being adopted in the superior Western world, however, without the benefit of the East Indian ingredients such as turmeric powder.

Circulating omega 3 fatty acids are lower in vegetarians and non-fish eaters than in people who consume fish, without any ill effects reported in pregnancy outcomes of East Indian vegetarians vs omnivores of North London and the Southwestern United States, and reported significantly less negative emotion compared with omnivores, despite the reduced levels of DHA. The apparent discrepancy between omnivores showing a clear cognitive impairment associated with reduced DHA and data showing improved mental health in East Indian vegetarians indicates a possible connection between the East Indian vegetarian diet containing turmeric powder along with other spices, and improved mental health in the



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<u>Home</u>	The Foundation	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	<u> Mana Sanskriti (Our Culture)</u>
<u>Vegetarian Links</u>	<u>Disclaimer</u>	Solicitation	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

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East Indian vegetarians. This assumption was proved by an article entitled, Curcumin boosts DHA in the brain: Implications for the prevention of anxiety disorders, by Wu et al. in Biochimica et Biophysica Acta. Curcumin can influence with its anti-inflammatory, antioxidant, neuroprotective, and monoaminergic effects, an array of biological activities, dysregulation of which results in several neuropsychiatric disorders. In a systematic review, in vitro, animal, and human studies investigating the potential of curcumin as a treatment for neuropsychiatric disorders such as major depressive disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), bipolar disorder, psychotic disorders, and autism, it was concluded that curcumin was a promising agent for many of these conditions. Currently, the greatest support for the efficacy of curcumin is for the treatment of the major depressive disorder.

Traumatic Brain Injury (TBI) is sustained from severe or mild damage to the brain tissue from injury thanks to military adventures of US around the world. Over 1.7 million people suffer annually from TBI and the consequent medical care costs exceed USD 70 billion, a good opportunity for the commercial military and pharmaceutical industry to reap the benefits of exploitation of the never-ending warfare strategically and symbiotically, producing military machinery, weapons of mass and chemical destruction, and pharmaceuticals, thereby creating necessary economic growth for the *Vaisya* (Commercial /Mercantile Complex), *Kshatriya* (Military Industrial Complex), and *Brahmin* (Religio-Cultural Complex) - "the Empire of US" around the globe providing jobs, protection, and charity for the *Shudra* (agriculturists, (il/legal) aliens, natives, artisans, and white/blue collor laborers, including black, brown, colored, yellow, white, mixed, and Jew / Gentile / Pagan / Indu - aka - Hindu -aka- Sindhu / Muslim / Christian / Chritian Downtrodden-aka-Dalits, criminals, outcastes, and homeless) at home in US, the Beacon of Hope of Shining Democracy on the Capitalist Hill, and around the world maintaining the *Dharma* (Law and Order).

What remains is that the pharmaceutical industry needs to solve the problem associated with the poor oral bioavailability of standard curcumin with innovative formulations, which may be the essence of the above-discussed EP2555787 (B1) granted recently in the EU having the global dossier EP 1890546 A1; EP 1890546 A4; JP 2008545740 A; JP 5039032 B2; US 20070148263 A1; US 7736679 B2; US 20080226755 A1; US 7883728 B2; US 20100217045 A1; US 7879373 B2; US 20110098361 A1; US 8197869 B2; US 20110092603 A1; US 8153172 B2; EP 2555787 A2; EP 2555787 A4; EP 2555787 B1; EP 3290045 A1; US 20120220666 A1; US 8623431 B2; US 20120207863 A1; US 8329233 B2; US 20140099390 A1; US 20140295005 A9; US 8859020 B2; US 20140088200 A1; US 8993013 B2; US 20140093594 A1; US 8895087 B2; US 20140193533 A1; US 9492402 B2; US 20140371327 A1; US 20150037442 A1; US 9861677 B2; US 20150157718 A1; US 9878040 B2; US 20160008479 A1; US

Issue 245

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<u>Home</u>	The Foundation	<u>Management</u>	The Andhra Journal of Industrial News	The Telangana Science Journal	Mana Sanskriti (Our Culture)
<u>Vegetarian Links</u>	<u>Disclaimer</u>	<u>Solicitation</u>	<u>Contact</u>	<u>VPC</u>	<u>Vedah-net</u>

Issue 245

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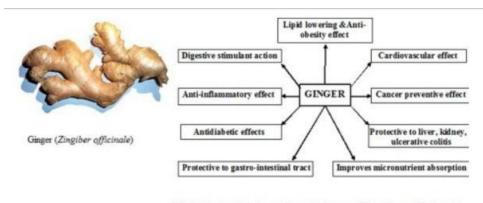
20160067300 A1; US 20170042833 A1; US 20170202785 A1; US 20170360869 A1; US 20180104339 A1.

Sharma et al., Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res.; 7(7): 1894-900 (2001 July). http://clincancerres.aacrjournals.org/content/7/7/1894.full-text.pdf

- 20 Health Benefits of Turmeric https://www.healthdiaries.com/eatthis/ 20-health-benefits- of-turmeric. html
- 15 Benefits of Turmeric Daily Health Life Styles
- 10 Benefits of Turmeric | Daily Natural Remedies | Turmeric Curcumin Supplements

Many dietary compounds such as apocarotenoid (saffron - *Cocus sativus*), curcumin, capsaicin (hot pepper), gingerols, allin and isoallin (onion- *Allium cepa*, garlic- *Allium sativum*), and resveratrol have been studied in *in vitro* and *in vivo* models of carcinogenesis as well as tested in early phase human clinical trials. Resveratrol, for example (3,5,4'-trihydroxy-*trans*-stilbene), is an antioxidant phytoalexin found in grapes, mulberries, peanuts, and *Cassia quinquangulata* plants that may help to protect against carcinogenesis and pathogenesis (see benefits of resveratrol attributed to alcohol "Alcohol, A Double-Edged Sword" and US6414037B1; US6211247B1; US6048903A; US6270780B1; US6572882B1; US6878751B1; US6358517B1).

For millennia, the rhizome of ginger (*Zingiber officinale Roscoe*) has been consumed worldwide as a herbal medicine for various diseases and conditions, alleviation of nausea, arthritis, and pain, and as a spice for nutrition. It is an important ingredient in Traditional Chinese Medicine (TCM) and Indian Ayurvedic Medicine.



Multiple health benefits of ginger (Zingiber officinale)

Issue 245

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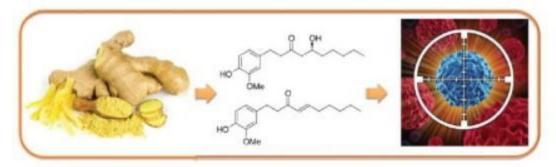
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Ginger contains pungent phenolic substances collectively known as gingerols. Other constituents include capsaicin, gingediol, galanolactone, gingesulfonic acid, galactosylglycerols, gingerglycolipids, diarylheptanoids, neral, monoacyldi-vitamins, paradols, phytosterols, zingerone, zingiberene, zingiberol, mono and sesquiterpenes, camphene, β -sesquiphellandrene, β -bisabolene, α -farmesene, curcumene, cineole, citral, terpineol, terpenes like phellandrene, borneol, β -elemene, zingiberenol, limonene, geraniol, linalool.



Gingerols and the corresponding shogaols are the major pungent compounds present in the rhizomes of fresh and dried ginger (*Zingiber officinale*), respectively. These compounds have a favourable toxicity profile, but are cytotoxic towards a range of cancer cell lines. Tumours induced in several animal models were successfully treated by gingerols.

Gingerol and its analogs are thermally labile and easily undergo dehydration reactions to form the corresponding shogaols that impart the characteristic pungent taste to dried ginger. Both gingerols and shogaols exhibit a host of biological activities, ranging from anticancer, antioxidant, antimicrobial, anti-inflammatory and anti-allergic to various central nervous system activities. Shogaols are also important biomarkers used for the quality control of many ginger-containing products. 6-Gingerol has been found to possess anticancer effect on a variety of biological pathways involved in apoptosis, cell cycle regulation, cytotoxic activity, and inhibition of angiogenesis. Due to its efficacy in the regulation of multiple targets, as well as its safety for human use, 6-gingerol has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various diseases (see also, Ginger rhizomes (*Zingiber officinale*): A spice with multiple health beneficial potentials; Patent Picks—Bioactive Ginger, Coumarin, Heat Shock Proteins and More for Wellness Cosmetics; US20050031772A1; US20030185918A1; DE19859499C2; DE102005062145A1; DE102004041716A1; GB0501654D0; WO2002041838A3; JP2629844B2; JP5375050B2; JP5906541B2; JP5086590B2; CN100395549C;

Issue 245

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CN102423309B; CN104436144B; CN105616442A; KR101324926B1). A three-phase partitioning (TPP), a bioseparation technique, based on the partitioning of polar constituents, proteins, and hydrophobic constituents in three phases comprising of water, ammonium sulfate and *t*-butanol may be used for extraction of oleoresin and gingerols from dry powder (Food Chemistry (1 February 2017)).

People with greater brain volume have been shown in studies to have better cognitive abilities. Having a brain volume that is 3.6 milliliters smaller is equivalent to one year of aging. A diet rich in vegetables, fruit, and nuts may help develop bigger brains, according to a study published in the May 16, 2018, online issue of *Neurology*. Therefore, initiatives that help improve diet quality may be a good strategy to maintain thinking skills in older adults. Researchers found after adjusting for age, sex, education, smoking and physical activity that a higher diet score was linked to larger total brain volume when taking into account head size differences. Those who consumed a vegetarian diet had an average of two milliliters more total brain volume than those who did not. The study is based on unverifiable self-reported responses to a questionnaire asking how much they ate of nearly 400 items over the past month.

According to a report in the Journal Nutrition (April 2017), daily ginger consumption was associated with decreased risk for hypertension and has a potential preventive property against hypertension and coronary heart disease.





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