



AAP Advances in Nutraceuticals

Flavonoids as Nutraceuticals



Rajesh K. Kesharwani | Deepika Saini
Raj K. Keservani | Anil K. Sharma
Editors



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Edited by

Rajesh K. Kesharwani, PhD

Deepika Saini, PhD

Raj K. Keservani, PhD, MPharm

Anil Kumar Sharma, PhD, MPharm

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ABOUT THE BOOK SERIES: AAP ADVANCES IN NUTRACEUTICALS

SERIES EDITORS:

Raj K. Keservani, PhD, MPharm

Faculty of B. Pharmacy, CSM Group of Institutions, Allahabad, India

Telephone: +91-7897803904

email: rajksops@gmail.com

Rajesh K. Kesharwani, PhD

Nehru Gram Bharati (Deemed to be University), Prayagraj, India

Anil K. Sharma, PhD, MPharm

Department of Pharmacy, School of Medical and Allied Sciences,
GD Goenka University, Gurugram, India

In the modern era, mankind has witnessed a paradigm shift with respect to fundamental eating behavior. The lack of physical workouts and busy schedules at offices and in households have promoted the consumption of junk foods, which eventually results in numerous diseases and disorders since the nutritional content from fast food is inadequate. Plumpness and obesity have become a global health threat. The leading causes of death from most developing nations are noncommunicable diseases such as cardiovascular diseases, cancer, arthritis, osteoporosis, and liver toxicity. Patients suffering from such lifestyle ailments are a bit apprehensive towards prolonged use of costly modern therapeutics, which encourages instead the use of alternative approaches for management of such diseases and disorders.

The emerging sector of the nutraceutical industry encompasses products derived from nature, dietary supplements, and functional foods. Nutraceuticals are used for treatment and prevention of a broad range of diseases, such as the common cold, arthritis, sleep-related disorders, cancers, cardiovascular complications, metabolic disorders, and others.

The research on nutraceuticals is increasing day by day, considering the beneficial effects of food or food supplements in the management of diverse

diseases. The issue of paramount concern is standardization and establishment of clinical efficacy of nutraceuticals, which is in fact a challenge for researchers around the globe.

This book series aims at realizing the significance of the variety of nutraceuticals for human well-being. The books in the series will also emphasize the role of dietitians and nutritionists for the prescription of judicious eating habits. The key food components such as carbohydrates, proteins, and lipids as well as micronutrients (vitamins, minerals) are demonstrated to maintain good health, obviating the need for medicines. Thus, nutraceuticals that are indeed derived from food ingredients are believed to be potential alternative therapeutics.

Asymptomatic diseases/disorders necessitate proper diagnosis. Stressed circumstances have been reported to cause weight loss. Workplace stress is a key variable in the genesis and propagation of metabolic disorders. The nuances of the underlying mechanisms are still to be deciphered. Poor lifestyle trends have been attributed along with the consumption of junk foods in several such instances. Sugar-rich carbonated beverages, the use of contraband drugs, and the consumption of liquor in excess are assigned as risk factors. This book series will cover advances and applications in addition to providing the basics of nutraceuticals.

The books in this series may be valuable resources for industry professionals to design and develop quality products for end users. In addition, the book series will be fortified by ideas of innovation, concept building, manufacturing aspects, quality control, and regulatory status of nutraceuticals.

Ostensibly, business has seen a rise in the nutraceutical consumption in recent years. Pure, safe, efficacious products are the need of the hour globally. There are a number of books on nutraceuticals in the market, yet these are only a few books presenting certain aspects of nutraceuticals therein. This book series aims to offer a holistic view of this promising strategy, which is picking up pace with time. This book series will be a unique endeavor to bring manufacturing, research and development, and marketing strategies under a single umbrella.

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Editors: Editors: Meenakshi Jaiswal, PhD, Raj K. Keservani, PhD, Rajesh K. Kesharwani, PhD, and Swati G. Talele, PhD

ABOUT THE EDITORS

Rajesh K. Kesharwani, PhD

*Associate Professor, Department of Computer Application,
Nehru Gram Bharati (Deemed to be University), Prayagraj, India*

Rajesh K. Kesharwani, PhD, MTech, is working as Associate Professor, Department of Computer Application, Nehru Gram Bharati (Deemed to be University), Prayagraj, India. He has more than 11 years of research and nine years of teaching experience at various institutes of India, imparting bioinformatics and biotechnology education. He has received several awards, including the NASI-Swarna Jayanti Puruskar by The National Academy of Sciences of India. He has supervised one PhD and more than 20 undergraduate and graduate students for their research work. Dr. Kesharwani has authored over 49 peer-reviewed articles, 20 book chapters, and 14 edited books with international publishers. He has been a member of many scientific communities as well as a reviewer for many international journals. He has presented many papers at various national and international conferences. He has been a recipient of a Ministry of Human Resource Development (India) Fellowship and a Senior Research Fellowship from the Indian Council of Medical Research, India. His research fields of interest are medical informatics, protein structure and function prediction, computer-aided drug designing, structural biology, drug delivery, cancer biology, nanobiotechnology, and biomedical sciences. Dr. Kesharwani received his PhD from the Indian Institute of Information Technology, Allahabad, and worked at NIT Warangal for two semesters.

Deepika Saini, PhD

*Assistant Professor, Department of Zoology, Chamanlal Mahavidyalaya,
Haridwar, Uttarakhand, India*

Deepika Saini, PhD, is currently working as Assistant Professor in the Department of Zoology at Chamanlal Mahavidyalaya, Haridwar, Uttarakhand, India. She has teaching experience of about five years. She has also

worked as an adjunct faculty member in the Natural Science Department of the University of Maryland Eastern Shore, Salisbury, Maryland, USA. She has published over 14 papers in national and international seminars and conferences and has also attended many workshops. She has also been awarded a Best Teacher Award 2020 by the Society of Research in Biological Studies. Dr. Saini serves as a reviewer and editorial board member for several international and national journals, including *American Journal of Life Sciences*, *International Journal of Zoology Studies*, *International Journal of Biological Studies*, among others. She has successfully edited four books. During the pandemic in 2020, she has organized webinars with reputed institutes, such as the Zoological Survey of India and the Botanical Survey of India. She has organized two national conferences funded by the Uttarakhand Council of Science and Technology, Dehradun and Uttarakhand Council for Biotechnology, Dehradun, India.

Raj K. Keservani, PhD, MPharm

Associate Professor, Faculty of B. Pharmacy, CSM Group of Institutions, Allahabad, India

Raj K. Keservani, PhD, MPharm, is a Faculty of B. Pharmacy, CSM Group of Institutions, Allahabad, India. He has more than 12 years of academic (teaching) experience from various institutes of India in pharmaceutical education. He has published over 30 peer-reviewed papers in the field of pharmaceutical sciences in national and international journals, more than 40 book chapters, three co-authored books, and 19 edited books, with several in the works now. He is also active as a reviewer for several international scientific journals. Dr. Keservani graduated with a pharmacy degree from the Department of Pharmacy, Kumaun University, Nainital (Uttarakhand), India. He received his Master of Pharmacy (MPharm) (specialization in pharmaceuticals) from the School of Pharmaceutical Sciences, Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, India. Dr. Keservani is a life member of Society of Pharmaceutical Education and Research (SPER). His research interests include nutraceutical and functional foods, novel drug delivery systems (NDDS), transdermal drug delivery/drug delivery, health science, cancer biology, and neurobiology.

Anil Kumar Sharma, PhD, MPharm

Assistant Professor, Department of Pharmacy, School of Medical and Allied Sciences, GD Goenka University, Gurugram, India

Anil Kumar Sharma, PhD, MPharm, is an expert in the area of pharmaceuticals with a background in drug delivery. He has taught these subjects for nearly 10 years at universities such as the Delhi Institute of Pharmaceutical Sciences and Research, the University of Delhi, and the School of Medical and Allied Sciences, G. D. Goenka University, India. Prior to taking up his current role in 2018, Dr. Sharma served in academic positions such as Lecturer (Pharmaceutics) at the Delhi Institute of Pharmaceutical Sciences and Research, University of Delhi, India. He has published over 28 peer-reviewed papers in the field of pharmaceutical sciences in both national and international journals as well as many book chapters and several edited books. He holds a PhD (Pharmaceutical Sciences) from the University of Delhi, an MPharmacy (Pharmaceutics) from the Rajiv Gandhi Pradyogiki Vishwavidyalaya and a BPharmacy from the University of Rajasthan.



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CONTRIBUTORS

V. Aswathy

Ethnomedicine and Ethnopharmacology Division, KSCSTE–Jawaharlal Nehru Tropical Botanic Garden and Research Institute, Palode, Thiruvananthapuram, Kerala, India

Ittishree Bhardwaj

G.V.M. College of Pharmacy, Sonipat, Haryana, India

Priyanka Bhardwaj

MD Scholar, Department of Sharir Rachana, CBPACS, New Delhi, India

Mandar Bhutkar

Department of Bioscience and Bioengineering, Indian Institute of Technology, Roorkee, Uttarakhand, India

B. S. Bijukumar

Post-Graduate, Department of Zoology and Research Center, Mahatma Gandhi College, Thiruvananthapuram, Kerala, India

Diwakar Chauhan

Department of Chemistry, School of Basic and Applied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

Monika Chauhan

Department of Forensic Science, School of Basic and Applied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

Niharika Dewangan

Kalinga University, Naya Raipur; Swami Shri Swaroopanand Saraswati Mahavidyalaya, Bhilai, Chhattisgarh, India

Nancy Gautam

Research Scholar, Department of Chemistry, Meerut College, Meerut, Uttar Pradesh, India

Ritu Kataria

G.V.M. College of Pharmacy, Sonipat, Haryana, India

Inderjeet Kaur

PG Department of Biotechnology, Lyallpur Khalsa College, Jalandhar, Punjab, India

N. M. Krishnakumar

Department of Biosciences, Rajagiri College of Social Sciences, Kalamassery, Kochi, Ernakulam, Kerala, India

Ajay Kumar

Department of Life Science, School of Basic and Applied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

Ashwani Kumar

Department of Pharmaceutical Sciences (FAMS), Gurukul Kangri Deemed University, Haridwar, Uttarakhand, India

Sunil Kumar

Gurukul Kangri Deemed University, Haridwar, Uttarakhand, India

Alka Mishra

Government VYTPG Autonomous College, Durg, Chhattisgarh, India

Harsh Mohan

Department of Forensic Science, School of Basic and Applied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

Chandrashekhar Murumkar

Post-Graduate Research Center, Department of Botany, Tuljaram Chaturchand College of Arts, Science, and Commerce, Baramati (Autonomous), Maharashtra, India

Keshari Nandan

Department of Chemistry, Gurukula Kangri (Deemed to be University), Haridwar, Uttarakhand, India

Preeti Panchal

G.V.M. College of Pharmacy, Sonipat, Haryana, India

Madhuri Patil

Post-Graduate Research Center, Department of Botany, Tuljaram Chaturchand College of Arts, Science, and Commerce, Baramati (Autonomous), Maharashtra, India

R. Prakashkumar

Ethnomedicine and Ethnopharmacology Division, KSCSTE–Jawaharlal Nehru Tropical Botanic Garden and Research Institute, Palode, Thiruvananthapuram, Kerala, India

Deepanshu Rana

Assistant Professor, Department of Microbiology, Sardar Bhagwan Singh University, Balawala, Dehradun, Uttarakhand, India

Ruchi Rani

Department of Bioscience and Bioengineering, Indian Institute of Technology, Roorkee, Uttarakhand, India

Pooja Sabharwal

Assistant Professor, PG Department of Sharir Rachana, CBPACS, Affiliated to GGSIP University New Delhi, India

Neha Saini

G.V.M. College of Pharmacy, Sonipat, Haryana, India

Parul Saini

Alumni, John Curtin School of Medical Research, Australian National University, Canberra, Australia

Pragati Saini

Department of Life Science, School of Basic and Applied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

Arun Dev Sharma

PG Department of Biotechnology, Lyallpur Khalsa College, Jalandhar, Punjab, India

Ankit Singh

Research Scholar, Department of Chemical Engineering, Rajiv Gandhi Institute of Petroleum Technology, Jais, Amethi, Uttar Pradesh, India

Shyam Vir Singh

Department of Chemistry, Shri Guru Ram Rai (PG) College, Pathribagh, Dehradun, Uttarakhand, India

Peeush Singhal

Department of Pharmaceutical Sciences (FAMS), Gurukul Kangri Deemed University, Haridwar, Uttarakhand, India

Ritu Vishnoi Singhal

Department of Botany, Chinmaya Degree College, Haridwar, Uttarakhand, India

S. R. Suja

Ethnomedicine and Ethnopharmacology Division, KSCSTE–Jawaharlal Nehru Tropical Botanic Garden and Research Institute, Palode, Thiruvananthapuram, Kerala, India

Shailly Tomar

Department of Bioscience and Bioengineering, Indian Institute of Technology, Roorkee, Uttarakhand, India



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ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
ACGs	apigenin, C-glycosides
AChE	acetylcholinesterase
AD	Alzheimer's disease
AGEs	advanced glycation end products
AIDS	acquired immune deficiency syndrome
AMPK	AMP-activated protein kinase
AP-1	activating protein-1
AQP4	aquaporin 4
AR	analytical reagents
ARDS	acute respiratory distress syndrome
ARE	antioxidant response element
AS	aureusidin synthase
ASFV	African swine fever virus
ATL	adult T-cell leukemia
ATP	adenosine triphosphate
BChE	butyrylcholinesterase
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CDKs	cyclin-dependent kinases
CE	capillary electrophoresis
CGH	comparative genomic hybridization
CH ₃	methyl group
CHI	chalcone isomerase
CHIKV	chikungunya virus
CHS	chalcone synthase
CoQ10	coenzyme Q10
CoV	coronavirus
COVID-19	coronavirus disease
COX	cyclo-oxygenase
CRP	reactive C-protein
CSI	chronic systemic inflammation
CV-B3	coxsackievirus B3
CVD	cardiovascular diseases
DCs	dendritic cells
DENV	dengue virus
DHAP	3-deoxy-D-arabino-heptulosonic acid-7-Phosphate

dsDNA	deoxyribonucleic acid
EAC	Ehrlich ascites carcinoma
EBV	Epstein-Barr virus
EGCG	epigallocatechin gallate
EGF	epidermal growth factor
EGFR	EGF receptor
ER	estrogen receptors
ERK1/2	extracellular signal-regulated kinases 1/2
EUFRIN	European Fruit Research Institutes Network
FISH	fluorescence in situ hybridization
GCG	gallic acid
GNP	gold nanoparticle-immobilized
GSH-Px	glutathione peroxidase
H2L	hit-to-lead
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	Huntington's disease
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HPV	human papillomavirus
HRV	human rhinovirus
HSD	3 β -hydroxysteroid dehydrogenase
HSV-1	herpes simplex virus type 1
HTLV	human T-cell lymphotropic virus type
IE	immediate-early
IFN- γ	interferon- γ
IgE	immunoglobulin E
IL	interleukin
iNOS	inducible nitric oxide synthase
IOM	Institute of Medicine
IRFs	interferon regulatory factors
I κ B	inhibitor of kappa B
JEV	Japanese Encephalitis Virus
KSHV	Kaposi's sarcoma-associated herpesvirus
LCMV	lymphocytic choriomeningitis virus
LPS	lipopolysaccharide
MAD	malondialdehyde
MAPK	mitogen-activated protein kinase
MAYV	Mayaro virus
MERS	middle east respiratory syndrome
MIP-2	macrophage inflammatory protein-2
Mpro	main protease
mRNA	messenger RNA

MS	multiple sclerosis
NAD ⁺	nicotinamide adenine dinucleotide
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NF- κ B	nuclear factor kappa B
NMN	nicotinamide mononucleotide
NMR	nuclear magnetic resonance
NO	nitric oxide
NR	nicotinamide-riboside
nsP1	non-structural protein 1
PAC	proanthocyanidin
PAH	pulmonary arterial hypertension
PAL	phenylalanine lyase
PBMC	peripheral blood mononuclear cell
PD	Parkinson's disease
PD-ACE-2	peptidase domain of ACE-2
PEP	phosphoenol pyruvate
PPAR α	peroxisome proliferator-activated receptor
PRRs	pattern recognition receptors
Rb	retinoblastoma
RBD	receptor binding domain
RNAs	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
rRNA	ribosomal RNA
RSV	respiratory syncytial virus
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory disease syndrome coronavirus-2
SFV	Semliki-forest virus
SOCS	suppressor of cytokine signaling
SOD	superoxide dismutase
STAT	signal transducer and activator of transcription
TBEV	tick-borne encephalitis virus
TF	transcription factors
TGFB	transforming growth factor B
Th2	T-helper type 2
TLR9	toll-like receptor 9
TMC	traditional Chinese medicine
TNF- α	tumor necrosis factor-alpha
tRNA	transfer RNA
UV	ultraviolet
VEGF	vascular endothelial growth factor
ViPR	virus pathogen database and analysis resource

VZV	varicella-zoster virus
WNV	West Nile virus
XO	xanthine oxidase
XRE	xenobiotic response element
YFV	yellow fever virus
ZIKV	ZIKA virus

PREFACE

People's lives have become so busy today, that everyone is rushing around without taking care of their health. This has given rise to many people experiencing health issues early on. In seeking treatment though, surveys have shown that people today are increasingly seeking ayurvedic and plant-derived remedies in comparison to allopathy due to their potential for reduced side effects, easy availability, and a range of health benefits.

Flavonoids are well-known plant metabolites which have come to researchers' attention due to their extraordinary properties in treating health issues. The pharmaceutical importance of flavonoids can be summarized in the fact that they are widely accepted as having anti-depressant and antioxidant properties, are antiviral as well as anti-inflammatory. They are also of great benefit when it comes to neuroprotection and cardiovascular disease. Nowadays, oncology and flavonoids have proven to be a great combination for many types of cancers.

This book, *Flavonoids as Nutraceuticals*, comprises 13 chapters that describe the use of flavonoids for the prevention and treatment of diseases and their mechanism.

Chapter 1, *Nutraceuticals: The New Anti-Aging Method*, written by Peeush Singhal et al., emphasizes the importance of anti-aging nutritional foods and discusses modern aging theories. In addition, it also describes the role of anti-aging nutrients, how dietary needs change with age and diet, food quality problems for the aging population, and the diet patterns of the elderly.

Chapter 2, *Introduction to Flavonoids*, written by Deepanshu Rana and his associates discusses about the flavonoid's classification and its significance. Neha Saini and her associates outline the uses of flavonoids and demonstrate that metabolomics is a useful means for studying flavonoid metabolism in various agricultural crops in Chapter 3, *Importance of Flavonoids in Agriculture*.

Despite many efforts, very few flavonoids are in clinical trials for antiviral treatment against various virus infections. Flavonoids have been explored as evidence-based natural sources of antivirals against a variety of virus classes in Chapter 4, *Therapeutic Antiviral Potential of Flavonoids*, written by Shally Tomar and her colleagues.

Priyanka Bhardwaj and Pooja Sabharwal describe the naturally occurring polyphenolic compounds – flavonoids as well-known for their ability to aid in the treatment of a variety of ailments as well as to mitigate the adverse effects of various treatment regimens in Chapter 5, *Regulation of Gene Expression by Flavonoids*.

Chapter 6, *Flavonoids of Asteraceae-Promising Anti-Inflammatory Agents*, written by S. R. Suja and colleagues, explores the role of flavonoids of plants of the Asteraceae family in combating several inflammatory processes underlying chronic disease conditions. S. R. Suja and associates focus on the immuno-enhancing potential of various bioactive flavonoids isolated from natural sources and their mechanism of action in Chapter 7, *Bioactive Flavonoids From Natural Sources: Potential Immune-Boosters*.

Chapter 8, *Role of Flavonoids as Anti-Inflammatory Agents*, incorporates current knowledge of the mechanisms involved in flavonoids' anti-inflammatory properties and the implications of these effects on protection against various chronic inflammatory diseases written by Parul Saini.

Monika Chauhan and her associates summarize how flavonoids have become an essential factor for a wide range of nutraceutical, pharmacological, cosmetic, therapeutic uses. However, due to the intricacy of flavonoids' existence in diverse food sources, the diversity of dietary culture, and the incidence of a vast quantity of flavonoids in nature, precisely quantifying daily flavonoids consumption remains a challenge in Chapter 9, *Current Trends in the Health Benefits of Flavonoids*.

The fastness of washing, rubbing, light, and perspiration of the fastness values for colored samples range from fair to outstanding, and this evaluation is also useful in the textile industry described in Chapter 10, *Analysis of Color Fastness Properties of Natural Dye Extracted From *Rhus parviflora* (TUNG) on Wool Fibers Using a Combination of Natural and Synthetic Mordants* by Shyam Vir Singh.

Chapter 11, *Flavonoids in Treating Pregnancy-Induced Disorders*, written by Niharika Dewangan and Alka Mishra, gives details about the effects of flavonoids on pregnancy disorders.

Chapter 12, *Flavonoids: Their Classes and Biosynthesis*, deals with the flavonoid's function and classification along with their biosynthesis, discussed by Madhuri Patil and Chandrashekhar Murumkar.

Flavonoids and their antiviral perspective against COVID-19 have been covered in Chapter 13, *Plant-Based Flavonoids as a Promising Tool to Combat COVID-19 Infection*, written by Arun Dev Sharma and Inderjeet Kaur.

CHAPTER 1

NUTRACEUTICALS: THE NEW ANTI-AGING METHOD

PEEUSH SINGHAL,¹ ASHWANI KUMAR,¹ RITU VISHNOI SINGHAL,²
and SUNIL KUMAR³

*¹Department of Pharmaceutical Sciences (FAMS),
Gurukul Kangri Deemed University, Haridwar, Uttarakhand, India*

*²Department of Botany, Chinmaya Degree College, Haridwar,
Uttarakhand, India*

³Gurukul Kangri Deemed University, Haridwar, Uttarakhand, India

ABSTRACT

At different times in life, people have different views on aging. As a process, aging not only affects the medical and economic levels at the individual level but also at the social and national levels. Aging is a natural process, but its standard definition in the healthcare field is unclear. Delaying the Aging process and maintaining a high quality of life until old age are the two most important goals. Various healthcare methods are being considered and tested to best regard aging as a disease. Nutritious food is a value-added dietary supplement product which has great potential to change the key structure and function of aging. Nutritional health products can be the key to changing the physiological and metabolic system abnormalities caused by aging. Nutraceuticals for Aging and anti-aging: Basic understanding and clinical evidence are based on 10 main challenges to address aging and anti-aging nutritional drugs, such as cognitive health, malnutrition, drug abuse, bladder control, and oral health. It explores how to supplement these challenges with nutritious foods and connects the application to the traditional

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wisdom of the aging process. The purpose of this chapter is to elucidate the significance of anti-aging dietary components and go over current views on ageing. Additionally, it discusses the function of anti-aging nutrients, how dietary requirements change as people age, issues with diet quality among the ageing population, and senior people's eating habits.

1.1 INTRODUCTION

The nutrients obtained from oral dietary ingredients are related to medical and health benefits (Dumoulin et al., 2016). In the past few decades, these ingredients have shown great potential in anti-aging effects by preventing or delaying the degeneration of skin cells (Bologna et al., 2012). For example, these factors can cause collagen and elastic fibers to degrade, leading to Aging. Digital internal and external factors cause degradation: biological progression of cells, tobacco, nutritional deficiencies, hormonal imbalances, and ultraviolet (UV) radiation (Ganceviciene et al., 2012; Parrado et al., 2019). The use of nutrients helps prevent skin roughness, skin elasticity and wrinkles, and pigmentation changes, all of which can lead to aging (Shamloul et al., 2019). Advances in skincare have greatly expanded the market for anti-aging nutrients. Some of the key nutrients that have been widely studied are amino acids, carotenoids (β -carotene, lutein, and zeaxanthin, and lycopene); fatty acids, minerals, polyphenols, and epigallocatechin gallate (EGCG) (Shamloul et al., 2019; Finch et al., 2010).

The connection between nutrition and aging has been extensively studied in animals and humans (Finch et al., 2010). Nutritional products are foods that have medicinal properties, which is why it's called a nutraceutical (Dhanjal et al., 2020). According to the definition in The Foundation for Medical Innovation, a nutraceutical is a meal that has medicinal price and offers fitness advantages, especially with inside the prevention and remedy of age-associated diseases (Bhowmik et al., 2013; Keservani et al., 2010a). That product includes realistic foods, dietary supplements (Keservani & Sharma, 2014), and herbal extracts, which give fitness advantages while fed overtime when fed as dietary supplements inside a diet plan (Himalian et al., 2021). Even researchers have encouraged that antioxidants have propitious consequences on each continual in addition to age-associated sicknesses, specifically neurodegenerative illnesses and maximum cancers (Hajhashemi et al., 2010). Various meals and dietary supplements (Keservani et al., 2020) that display an antioxidant capacity, which encompasses carotenoids,

flavonoids, and nutrients, prevent and address ROS-related continual situations, which end up in more healthy and longer lifespans (Hajhashemi et al., 2010). Food dietary supplements produce antagonistic outcomes in opposition to the degenerative and inflammatory strategies inside the frame and feature beneficial results on the immune and digestive system, therefore enhancing the fine of life (Rinninella et al., 2019). The present-day evaluation focuses on highlighting the manifestations of developing vintage and theories associated with developing older. Additionally, it additionally discusses the importance of weight loss plan control in aging and practical meals, in addition to nutraceuticals with anti-aging potential (Carocho & Ferreira, 2013; Keservani et al., 2010b).

1.2 WHY DO YOU AGE?

Gerontology, the look at growing old, can be an exceedingly new technological know-how that has made splendid development over the last 30 years. In the past, scientists searched for one theory that defined getting old but has found out that getting older may be a complex interplay of genetics, chemistry, physiology, and conduct. There at the moment are dozens of theories of aging to explain this inevitable truth of being human (Kirkwood & Austad, 2000).

1.2.1 PROGRAMMED THEORIES OF AGING

Programmed theories state that the human body is intended to age, and there is a sure organic course of events that bodies follow. These hypotheses share the possibility that maturing is normal and “modified” into the body (Goldsmith, 2016; Sikora, 2014; Laughrea, 1982).

There are a couple of various programmed theories of maturing:

1. **Programmed Longevity Theory:** It is the idea that maturing is brought about by specific genes turning on and off after some time.
2. **Endocrine Theory:** It is the possibility that standard changes in hormones control maturing.
3. **Immunological Theory:** Expresses that the safe framework is modified to decay after some time, leaving individuals more vulnerable to sicknesses.

1.2.2 ERROR THEORIES OF AGING

Error theories attest that maturing is brought about by ecological harm to the body's frameworks, which aggregates over time (Curtis, 1971).

There are a few error theories of maturing:

1. **Wear and Tear Theory:** This asserts that cells and tissues basically wear out.
2. **Pace of Living Theory:** It is the possibility that the quicker a living being utilizes oxygen, the more limited it lives.
3. **Cross-Linking Theory:** It states that cross-connected proteins gather and dial back the body's processes.
4. **Free Radicals Theory:** It asserts that free radicals in the climate cause harm to cells, which in the end impedes their function.
5. **Somatic DNA Damage Theory:** It is the possibility that hereditary transformations cause cells to break down.

1.2.3 GENETIC THEORY OF AGING

Studies have exhibited that hereditary qualities can assume a significant part in maturing. In one review, when scientists eliminated cells containing certain qualities from the organs of mice, they had the option to broaden the life expectancy of the creatures by as much as 35%. The significance of these analyses for people isn't known. However, analysts believe that hereditary qualities represent a large part of the variety in maturing among individuals (Chipalkatti et al., 1983).

Some vital ideas in hereditary qualities and maturing include:

1. **Longevity Genes:** These are explicit qualities that help an individual live more.
2. **Cell Senescence:** It is the interaction by which cells disintegrate over time.
3. **Telomeres:** These are structures on the finish of DNA that, in the long run, are drained, bringing about cells stopping to recreate.
4. **Stem Cells:** These are cells that can turn out to be any kind of cell in the body and hold a guarantee to fix harm brought about by maturing.

1.2.4 BIOCHEMICAL THEORY OF AGING

Regardless of qualities you have acquired, your body is persistently going through complex biochemical responses. A portion of these responses cause harm and, eventually, maturing in the body. Concentrating on these perplexing responses is assisting scientists with seeing how the body changes as it ages (Li et al., 2005).

Significant ideas in the biochemistry of maturing include:

- 1. Free Radicals:** These are unsteady oxygen molecules that can harm cells.
- 2. Protein Cross-Linking:** It means that abundance of sugars in the circulation system can make protein particles, in a real sense, stay together.
- 3. DNA Repair:** It is the idea that, for obscure reasons, the frameworks in the body that maintain DNA appears to turn out to be less powerful in older people.
- 4. Heatshock Proteins:** These are proteins that assist cells with enduring pressure and are available in less numbers in older individuals.
- 5. Hormones:** These change as we age, causing many changes in organ frameworks and different capacities.

1.3 ANTI-AGING BEHAVIORS

Fortunately, a significant number of the reasons for maturing that might be going on rashly can be altered through your behaviors (Wengreen et al., 2009).

The following are a couple of approaches to keep your body feeling as youthful as could really be expected:

- Eat food varieties stacked with antioxidants to limit harm brought about by free radicals.
- Exercise consistently to restrict bone and muscle loss.
- Keep your cholesterol low so you can slow the solidifying of your arteries and ensure your heart.
- Practice mental wellness to keep your mind sharp.
- Eventually, maturing is unavoidable. Deal with your body and brain and embrace the progressions.

1.4 DIET QUALITY ISSUES FOR AGING POPULATION

Tucker remarked that the focus of her Research would be on how dietary needs change with Aging, which nutrients in particular are important for Aging populations, and the challenge of achieving access to and consumption of a high-quality diet given the obstacles already discussed by other speakers (e.g., loss of appetite, oral health decline, mobility constraints) (Drewnowski & Warren-Mears, 2001).

1.5 HOW DIETARY NEEDS CHANGE WITH AGING?

Dietary requirements change with maturing in more ways than one (Lyubomirsky et al., 1999):

- People become less dynamic, their digestion eases back, their energy necessity diminishes, all of which imply that they need to eat less.
- Recent research shows that on the grounds that more established grown-ups' capacities to ingest and use numerous supplements become less proficient, their supplement prerequisites (especially as a component of weight) really increment. Tucker referenced that the last arrangement of nourishment suggestions given by the Institute of Medicine (IOM) incorporated separate proposals for individuals aged 70 or more consequently (IOM, 2006).
- Tucker noticed that, as a portion of the past researcher had examined, ongoing conditions and drugs can influence sustenance prerequisites. For instance, notwithstanding drug-supplement associations influencing drug digestion, some medication supplement connections are additionally supplementing squandering. This is particularly valid for the B nutrients (Wysocki & Pelchat, 1993).
- Keeping a supplement-thick eating routine is basically significant for older adults due to the effect of food admission on well-being. Long periods of examination have shown that diet quality hugely affects the state of being, intellectual condition, bone well-being, eye well-being, vascular capacity, and the safe framework. However, this can be trying to accomplish for several reasons.
- As Pelchat talked about, maturing is frequently joined by a deficiency of hunger and changes in taste and smell, all of which can prompt more restricted food decisions and lower admission of refreshing food varieties (Wysocki & Pelchat, 1993).

- As Jensen talked about, maturing is additionally regularly joined by a broad oral well-being decrease and a diminished capacity to swallow, which can influence food decisions and admission (Jensen, 2019).
- Many older adults experience versatility limitations, which make it hard to search for food, lift substantial containers, open holders, and so forth.
- As both Wellman and Kinsella referenced, low income is common in maturing populaces, making it hard for some older adults to get to great food sources (i.e., on the grounds that those food sources will in general be more costly) (Pillsbury, 2010).

1.6 A MODIFIED FOOD GUIDE PYRAMID FOR OLDER ADULTS

Due to the changing dietary needs of older adults, Tucker's colleagues on the Jean Meyer USDA HRNCA evolved what they termed the modified food Pyramid for older adults (Schipper et al., 2008). Key changes to the original USDA meals manual pyramid consist of the placement of water at the bottom of the pyramid due to the fact many older adults no longer drink sufficient water to stay hydrated and the site of a flag at the top of the pyramid indicating the want for calcium, nutrition D, and vitamin B12 dietary supplements because many older adults do not get sufficient of these vitamins in a standard diet. After an update to the food manual pyramid befell for the general population, Tucker's colleagues also created a brand-new modified MyPyramid for older adults with illustrated examples of healthy meals in every food organization (Newby et al., 2003). Key changes to the original MyPyramid consist of the addition of examples of physical activity at the lowest of the pyramid. More physical activity lets in for the intake of larger portions of food, which in flip increases the likelihood that every one of the vital vitamins will be fed. Also, physical pastime enables keep muscle mass with aging.

1.7 DIETARY PATTERNS OF OLDER ADULTS

Of path, no longer all older adults follow the tips of the changed MyPyramid. Tucker mentioned the sort of methods that older adults consume. She and her colleagues had been inspecting dietary patterns in older adults as a part of the Baltimore Longitudinal look at growing older. They recognized five eating styles: “white bread” (human beings that reap significantly more power intake from white bread [16%, on average] relative to other patterns), “wholesome” (higher strength consumption from fruit, high fiber cereal, and