NANOPHARMACEUTICALS

EXPECTATIONS AND REALITIES OF MULTIFUNCTIONAL DRUG DELIVERY SYSTEMS VOLUME 1

Edited by

RANJITA SHEGOKAR, PhD
Capnomed GmbH, Zimmern, Germany

ELSEVIER

Elsevier
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-817778-5

Publisher: Andre Gerhard Wolff
Acquisition Editor: Erin Hill-Parks
Editorial Project Manager: Pat Gonzalez
Production Project Manager: Punithavathy Govindaradjane
Cover Designer: Mark Rogers

Typeset by TNQ Technologies

Index

Note: 'Page numbers followed by "f" indicate figures and "t" indicates tables'.

A

Adsorption, distribution, metabolism, and elimination (ADME) studies, 121–122, 128
Alzheimer disease, 177–178
Antigen-presenting cells (APCs), 136
Autism, 180

B

BCS. *See* Biopharmaceutics classification system (BCS)
Bioactive compounds
  biochemical barriers, 21–22
  biological barriers, 21–22
  complexity, 20–21
  nanocarriers, 22–29, 23t–25t
    biokinetic profile, 33, 34t–35t
    cellular uptake capability, 29–32
    challenges, 33–37, 36t
    herbal nanoparticles for breast cancer, 34–37
    lipid-based nanocarrier systems, 22–29
    safe-by-design bioactive-loaded nanocarrier system, 29, 31t
    surface modification, 32
  physical barriers, 21, 21f
  therapeutic agents, 17–20
    Curcuma, 17–18
    *Gnetum gnemon L. (*Gg*)*, 19–20, 20f
    Physalis angulata L., 20, 20f
    Silybum marianum (L.), 19, 19f
    Zingiber officinale, 18–19
Biokinetic profile, 33, 34t–35t
Biopharmaceutics classification system (BCS), 152–153
Botulism, 142
Brain disorders, 176t, 177–182
  Alzheimer disease, 177–178
  autism, 180
  cerebral palsy, 180–181
  meningitis, 181
  migraine, 179
  myasthenia gravis, 181
  Parkinson disease (PD), 178
  schizophrenia, 179–180
  stroke, 182
  symptomatic drug, 178
  targeted drug, 178
Brain toxicity, 127

C

Cellular uptake capability, 29–32
Chemo-angiogenic therapy, 62
Chemo-enzyme prodrug therapy, 64–65
Chemo-immunotherapy, 61–62
Chemo-photothermal therapy, 63
Chemo-radiotherapy, 64
Copper (Cu) nanoparticles, 85
Coprecipitation (CP) technique, 108–109
Critical micelle concentration (CMC), 47
Cryogenic processing, 107
Curcuma, 17–18

D

Dasatinib (DAS), 55
Dendrimers, 192–193, 193f
Dermal toxicity, 126–127
Differential scanning calorimetry (DSC), 7
Drug-loading methods, 49

E

Electrostatic spinning, 109–111, 110f
Encapsulation parameters, 5
Enzyme inhibitor, 184
Ethosomes, 76–78
Eutectic mixtures, 98, 98f

F

Fifth generation, 96–97
First generation, 92–93
Fluid-bed coating, 111
Fourth generation, 95–96, 96f
Freeze drying, 106–107

G

Generally Recognized as Safe status (GRAS), 2–3
Genotoxicity, 126
Glass solution, 97–98
*Gnetum gnemon L. (*Gg*)*, 19–20, 20f
Gold (Au) nanoparticles, 82–83

H

High pressure homogenizers (HPH), 2–3
High-throughput screening (HTS), 54
Hot melt extrusion (HME), 112–114, 113f
Hydrophilicity/hydrophobicity properties, 55
Hydrophilic-lipophilic balance (HLB) values, 8

I

Immune responses after vaccination, 136–137
Immunotoxicity, 126
Inorganic nanoparticles, 80–86, 187, 190t
  gold (Au) nanoparticles, 82–83
  metal oxide nanoparticles, 83–84
  silver (Ag) nanoparticles, 80–82
Intellectual property (IP) landscape
  emerging trends, 220–226, 221f
  industry trends, 203–205, 204f
  monitoring strategies, 226–227
  oral drug delivery trends, 206–212
    disease areas, 210–212, 210f
    pharmaceutical substances, 210–212, 210f
    technologies, 208–210, 209f
  overview, 202–206

Intellectual property (IP) landscape (*Continued*)
parenteral drug delivery trends, 215–220
disease areas, 219–220
overall trends, 216–218
pharmaceutical substances, 219–220
technologies, 218–219, 218f
technology trends, 205–206, 206f
topical drug delivery trends, 212–215
disease areas, 214–215
overall trends, 212
pharmaceutical substances, 214–215
technologies, 212–214
Intranasal route, 176–177
In vitro assay interferences, 125–126
In vitro toxicity, 124–125

K

KinetiSol technique, 115–116

L

Lipid-based nanocarrier systems, 22–29
liposomes, 24–26
nanoemulsions, 26–27, 28t
solid lipid nanoparticles (SLNs), 28–29, 30t
Lipid nanocarriers, oral drug delivery
biopharmaceutics classification system (BCS), 152–153
classification and composition, 153–155, 154t
future perspectives, 168
gastrointestinal tract (GIT) irritation, 155
mechanisms with cell membranes, 166–168
nonvesicular lipid nanocarriers, 156–164
permeability enhancement strategies, 164–166, 165f
safety, 155
solubility enhancement strategies, 164–166, 165f
types, 155–164
vesicular lipid nanocarriers, 155–156
Lipid nanoparticles, 1–2, 74–79, 186–187, 186f
Liposomes, 74, 75t–76t, 137–141, 187–190, 191f, 191t
Liver toxicity, 127
Lyophilization, 106–107

M

Melt agglomeration, 114–115, 115f
Melting method, 111–116
Melting-solvent method, 116
Metal and nonmetal inorganic NPs, 142
Metallic NPs (MeNPs), 146–147
Metal oxide nanoparticles, 83–84
cerium oxide nanoparticles, 84
iron oxide nanoparticles, 83–84
titanium dioxide nanoparticles, 84
zinc oxide NPs (ZnONPs), 83
Molecular mobility, 100
Multidrug resistance (MDR), 49–54, 50f
chemotherapeutics codelivery, 49–54, 50f
chemosensitizers, 51–53, 52t
downregulating gene agents, 53–54

N

Nanocarriers, 22–29, 23t–25t
biokinetic profile, 33, 34t–35t
cellular uptake capability, 29–32
challenges, 33–37, 36t
herbal nanoparticles for breast cancer, 34–37
lipid-based nanocarrier systems, 22–29
safe-by-design bioactive-loaded nanocarrier system, 29, 31t
surface modification, 32
Nanocytotoxicity, 146–147
Nanoemulsions, 78–79, 190–192, 192t
Nanomedicines, 122–124
Nanoparticle-based vaccines
antigen-presenting cells (APCs), 136
companies and clinical trials, 143–146, 146t
immune responses after vaccination, 136–137
liposomes, 137–141
metal and nonmetal inorganic NPs, 142
metallic NPs (MeNPs), 146–147
nanocytotoxicity, 146–147
polymeric NPs, 142–143
vaccine types, 136t, 137, 138t–139t
virus-like particles (VLPs), 141–142
Nanoparticulate systems, wound healing
copper (Cu) nanoparticles, 85
ethosomes, 76–78
inorganic nanoparticles, 80–86
gold (Au) nanoparticles, 82–83
metal oxide nanoparticles, 83–84
silver (Ag) nanoparticles, 80–82
lipid-based nanoparticles, 74–79
liposomes, 74, 75t–76t
nanoemulsions, 78–79
nanostructured lipid carriers, 79
penetration enhancer vesicles (PEVs), 76, 77t
selenium nanoparticles, 86
silicon nanoparticles, 85–86
solid lipid nanoparticles, 79
stages, 74–79, 75f
transfersomes, 78
Nanotoxicity
absorption, 122–124
adsorption, distribution, metabolism, and elimination (ADME) studies, 121–122, 128
brain toxicity, 127
dermal toxicity, 126–127
drug delivery systems (DDSs), 121
drug molecules, 122–123
engineered nanomaterials, 123–124
genotoxicity, 126
immunotoxicity, 126
liver toxicity, 127
nanomedicines, 122–124
nanotechnology products regulation, 129
nephrotoxicity, 127
organ-on-chip systems, 128
perspectives, 129
pharmacokinetics of nanoparticles, 122f
risk assessment process, 124
theranostics, 122–124
in vitro assay interferences, 125–126
in vitro toxicity, 124–125
in vivo of human response, 127–128
whole-animal models, 128–129
Nasal and pulmonary delivery, 11
Nasal cavity anatomy, 182
Nephrotoxicity, 127
Neuronal pathway, 182–183

Nonvesicular lipid nanocarriers, 156–164
lipid nanoparticles, 162
microemulsions, 156–157
nanoemulsions, 157
nanostructured lipid carriers (NLCs), 163
self-emulsifying drug delivery systems (SEDDSs), 158
self-microemulsifying drug delivery systems (SMEDDSs), 158–159
self-nanoemulsifying drug-delivery systems (SNEDDSs), 159
smartLipids particles, 164
solid lipid nanoparticles (SLNs), 79, 162
solid self-emulsifying drug delivery systems (S-SEDDSs), 160
Nose-to-brain drug delivery
brain disorders, 176t, 177–182
Alzheimer disease, 177–178
autism, 180
cerebral palsy, 180–181
meningitis, 181
migraine, 179
myasthenia gravis, 181
Parkinson disease (PD), 178
schizophrenia, 179–180
stroke, 182
symptomatic drug, 178
targeted drug, 178
central nervous system (CNS) acting, 175–177
clinical trials, 194
intranasal route, 176–177
nasal absorption strategies, 183–184
enzyme inhibitor, 184
permeation enhancer, 183–184
nasal cavity anatomy, 182
nose-to-brain drug transport pathways, 182–183
neuronal pathway, 182–183
olfactory nerve pathway, 183
trigeminal sensory nerve pathway, 183
vascular pathway, 183
novel drug delivery approaches, 184–193
dendrimers, 192–193, 193f
inorganic nanoparticles, 187, 190t
lipidic nanoparticles, 186–187, 186f
liposomes, 187–190, 191f, 191t
nanoemulsions, 190–192, 192t
polymeric nanoparticles, 184–185

O

Ocular delivery, 9
Olfactory nerve pathway, 183
Organ-on-chip systems, 128

P

Parenteral administration, 10–11
Parkinson disease (PD), 178
PEGSS-C18 copolymer, 59
Penetration enhancer vesicles (PEVs), 76, 77t
Permeation enhancer, 183–184
Pharmacokinetics of nanoparticles, 47f
PH-sensitive codelivery systems, 57–58
Physalis angulata L., 20, 20f
Polymeric nanomicelles
application, 60–65
characterization, 46–49
techniques, 48–49
chemo-angiogenic therapy, 62
chemo-enzyme prodrug therapy, 64–65
chemo-immunotherapy, 61–62
chemo-photothermal therapy, 63
chemo-radiotherapy, 64
chemotherapeutics codelivery, 49–56
dasatinib (DAS), 55
Dox, 54–55
high-throughput screening (HTS), 54
hydrophilicity/hydrophobicity properties, 55
mitigate side effects, 56
multidrug resistance (MDR), 49–54, 50f
critical micelle concentration (CMC), 47
drug-loading methods, 49
micelles, 46–49
preparation methods, 47–48
principles, 46–49
reticuloendothelial system (RES), 47
stimuli-responsive codelivery, 56–59, 58t
PEGSS-C18 copolymer, 59
pH-sensitive codelivery systems, 57–58
redox-sensitive codelivery systems, 58–59
targeted codelivery, 60
transactivator of transcription (TAT), 60
Polymeric nanoparticles, 142–143, 184–185

R

Reconstructed human epidermis (RhE) technology, 8–9
Redox-sensitive codelivery systems, 58–59
Reticuloendothelial system (RES), 47
Risk assessment process, 124

S

Safe-by-design bioactive-loaded nanocarrier system, 29, 31t
Second generation, 93–95
Selenium nanoparticles, 86
Silicon nanoparticles, 85–86
Silver (Ag) nanoparticles, 80–82
Silybum marianum (L.), 19, 19f
Solid dispersions (SD)
applications, 99
challenges, 99–101
classification, 92–97, 92f–93f
drug release mechanism, 98–99
fifth generation, 96–97
first generation, 92–93
fourth generation, 95–96, 96f
melting method, 101, 111–116
hot melt extrusion (HME), 112–114, 113f
KinetiSol technique, 115–116
melt agglomeration, 114–115, 115f
melting-solvent method, 116
melt-solvent methods, 102
molecular mobility, 100
second generation, 93–95
solvent evaporation method, 102–111
coprecipitation (CP) technique, 108–109
cryogenic processing, 107
electrostatic spinning, 109–111, 110f
fluid-bed coating, 111
freeze drying, 106–107
lyophilization, 106–107

Solid dispersions (SD) (*Continued*)
spray drying, 103–106, 104f–105f, 105t
supercritical fluid (SCF) technology, 107–108
vacuum drying, 106
solvent method, 101
structure-based classification, 97–98
eutectic mixtures, 98, 98f
glass solution, 97–98
solid solutions, 97, 97f
techniques, 101–116
third generation, 95–96
administration routes, 8–11
drug bioavailability, 8–11
nasal and pulmonary delivery, 11
ocular delivery, 9
oral administration, 9–10
parenteral administration, 10–11
reconstructed human epidermis (RhE) technology, 8–9
topical and dermal routes, 8–9
drug delivery systems, 1–2
emulsifiers and polymers, 1–2
high pressure homogenizers (HPH), 2–3
hydrophilic-lipophilic balance (HLB) values, 8
lipid nanoparticles, 1–2
microemulsion, 2–3
nanotoxicology, 3
physicochemical properties, 5–8
differential scanning calorimetry (DSC), 7
encapsulation parameters, 5
particle morphology, 7
particle size, 6
release profile, 7–8
stability of formulations, 7–8
zeta potential, 6
preclinical toxicological studies, 3
solidified emulsion technologies, 2–3
toxicity profiling, 3–5
Solid solutions, 97, 97f
Solvent evaporation method, 102–111
coprecipitation (CP) technique, 108–109
cryogenic processing, 107
electrostatic spinning, 109–111, 110f
fluid-bed coating, 111
freeze drying, 106–107
lyophilization, 106–107
spray drying, 103–106, 104f–105f, 105t
supercritical fluid (SCF) technology, 107–108
vacuum drying, 106
Spray drying, 103–106, 104f–105f, 105t
Stability of formulations, 7–8
Supercritical fluid (SCF) technology, 107–108
Surface modification, 32

T

Theranostics, 122–124
Third generation, 95–96
Toxicity profiling, 3–5
Transactivator of transcription (TAT), 60
Transfersomes, 78
Trigeminal sensory nerve pathway, 183

V

Vacuum drying, 106
Vascular pathway, 183
Virus-like particles (VLPs), 141–142

W

Whole-animal models, 128–129
Wound healing, 73–74, 75t, 76t, 77t, 78–86

Z

Zeta potential, 6
Zingiber officinale, 18–19

Contributors

Hend Abd-Allah Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt

Mona Abdel-Mottaleb Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt; PEPITE EA4267, Univ. Bourgogne Franche-Comté, Besançon, France

Annis Catur Adi Faculty of Health, University of Airlangga, Surabaya, Indonesia

Mukta Agrawal Rungta College of Pharmaceutical Sciences and Research, Bhilai, Chhattisgarh, India

Amit Alexander Rungta College of Pharmaceutical Sciences and Research, Bhilai, Chhattisgarh, India

Mahavir Bhupal Chougule Translational Biopharma Engineering Nanodelivery Research Laboratory, Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, University, MS, United States; Pii Center for Pharmaceutical Technology, Research Institute of Pharmaceutical Sciences, University of Mississippi, University, MS, United States; National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, University of Mississippi, University, MS, United States

Juan Bueno Research Center of Bioprospecting and Biotechnology for Biodiversity Foundation (BIOLABB), Armenia, Quindío, Colombia

J.R. Campos Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra (FFUC), Pólo das Ciências da Saúde, Coimbra, Portugal

Anne Marie Clark CAS, a Division of the American Chemical Society, Columbus, OH, United States

Diana Diaz-Arévalo Molecular Biology and Immunology Department, Fundación Instituto de Inmunología de Colombia-FIDIC, School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, DC, Colombia

Riham I. El-Gogary Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt

N.B. Jadav Centre for Pharmaceutical Engineering Sciences, Faculty of Life Sciences, University of Bradford, Bradford, United Kingdom

Anđelka B. Kovačević Department of Pharmaceutical Technology, Institute of Pharmacy, Faculty of Biological Sciences, Friedrich-Schiller University Jena, Jena, Germany

Atsarina Larasati Research Center for Nanosciences and Nanotechnology, Bandung Institute of Technology, Bandung, Indonesia

Peter Mattei CAS, a Division of the American Chemical Society, Columbus, OH, United States

Maha Nasr Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt

A. Paradkar Centre for Pharmaceutical Engineering Sciences, Faculty of Life Sciences, University of Bradford, Bradford, United Kingdom

Heni Rachmawati School of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia; Research Center for Nanosciences and Nanotechnology, Bandung Institute of Technology, Bandung, Indonesia

Kobra Rostamizadeh Zanjan Pharmaceutical Nanotechnology Research Center, Zanjan University of Medical Sciences, Zanjan, Iran; Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, United States

A. Santini Department of Pharmacy, University of Napoli "Federico II", Napoli, Italy

Shailendra Saraf University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India

Swarnlata Saraf University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India

P. Severino Universidade Tiradentes (Unit), Aracaju, Sergipe, Brazil; Instituto de Tecnologia e Pesquisa, Laboratório de Nanotecnologia e Nanomedicina (LNMed), Aracaju, Sergipe, Brazil; Tiradentes Institute, Dorchester, United States

Ranjita Shegokar Capnomed GmbH, Zimmern, Germany

A.M. Silva School of Biology and Environment, University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal; Centre for Research and Technology of Agro-Environmental and Biological Sciences (CITAB), University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal

S.B. Souto Department of Endocrinology, S. João Hospital, Alameda Prof. Hernâni Monteiro, Porto, Portugal

E.B. Souto Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra (FFUC), Pólo das Ciências da Saúde, Coimbra, Portugal; CEB - Centre of Biological Engineering, University of Minho, Braga, Portugal

Asur Srinivasan CAS, a Division of the American Chemical Society, Columbus, OH, United States

Amanda Starling-Windhof CAS, a Division of the American Chemical Society, Columbus, OH, United States

Tina Tomeo CAS, a Division of the American Chemical Society, Columbus, OH, United States

Vladimir P. Torchilin Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, United States

Mingtao Zeng Center of Emphasis in Infectious Diseases, Department of Molecular and Translational Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX, United States

CHAPTER

2

Role of nanocarriers and their surface modification in targeting delivery of bioactive compounds

Heni Rachmawati[1,2], *Atsarina Larasati*[2], *Annis Catur Adi*[3], *Ranjita Shegokar*[4]

[1]School of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia; [2]Research Center for Nanosciences and Nanotechnology, Bandung Institute of Technology, Bandung, Indonesia; [3]Faculty of Health, University of Airlangga, Surabaya, Indonesia; [4]Capnomed GmbH, Zimmern, Germany

1. Bioactive compounds as promising therapeutic agents

Apart from their typical other uses, plants are a potential source for medicinal purposes. The exploration of therapeutic functions of substances present in plants has been done since long before prehistoric age. The practical reasons of traditional ways of medicine using plant materials for a wide range of human ailments are increase in population, insufficient drug supplies, prohibitive cost of treatments, adverse effects of several synthetic drugs, and development of resistance to currently used agents for communicable diseases.

According to the World Health Organization, around 80% of people worldwide depend on medicinal plants, in some cases for their primary health care, and around 21,000 plant species show potential benefits for human health and are listed in various databases [1]. The continuing interest in exploring health benefits of plants is evidence of the safety or minimal adverse events of herbal medicines, a part of the nature sync belief. A few of the species that contain important antioxidants to cure a wide range of diseases and have proven safe for long-term use are described in this chapter, including *Curcuma* sp, *Zingiber* sp, *Silybum marianum* L, *Gnetum gnemon*, and *Physalis angulate*.

1.1 *Curcuma* sp

Curcuma genus is classified under the family Zingiberaceae. The genus consists of more than 80 species [2]. They grow abundantly in Asia, including Southeast Asia, China, India, New Guinea, and Northern Australia [3]. All *curcuma* sp have similar flower spikes that arise from the top of the pseudo stem or sometimes on a

https://doi.org/10.1016/B978-0-12-817778-5.00002-6

separate stem directly from the rhizome. They differ mainly in the inner part of rhizomes, which vary in color, i.e., white, cream, yellow, orange, blue, bluish-green, and black [3]. In the family of curcuma, particularly the rhizomes show economic potential both for food and medicine. For many years, the rhizomes of *curcuma* have been used for food additives, spice, and condiments. More importantly, the potential therapeutic value of curcuma's rhizomes are reported elsewhere to cure various pathological conditions, including cancer [4–11]. Various species of *Curcuma* have been studied and reported such as *Curcuma amada Roxb*, *Curcuma aromatica*, *Curcuma caesia Roxb*, *Curcuma longa*, *Curcuma manga*, *Curcuma purpurascens*, *Curcuma xanthorriza*, and *Curcuma zedoria*. Plants belonging to the genus *Curcuma* are gaining importance worldwide and are an interesting topic for investigation and exploration. The plants contain bioactive molecules with various biological activities such as antiinflammation, antimicrobe, anti hypercholesterolemia, antirheumatic, antivirus, antifibrosis, antivenomous, antihepatotoxicity, antidiabetes, anticancer, and gastroprotector (Fig. 2.1).

The common phytoconstituents found in *Curcuma* are phenols, flavonoids, alkaloids, terpenoids, tannins, saponins, steroids, glycosides. Among other phytoconstituents in *Curcuma*, xanthorrizhol and curcuminoid are two important substances showing similar bioactivities and many health-promoting benefits, are being widely explored for therapeutic purposes [12].

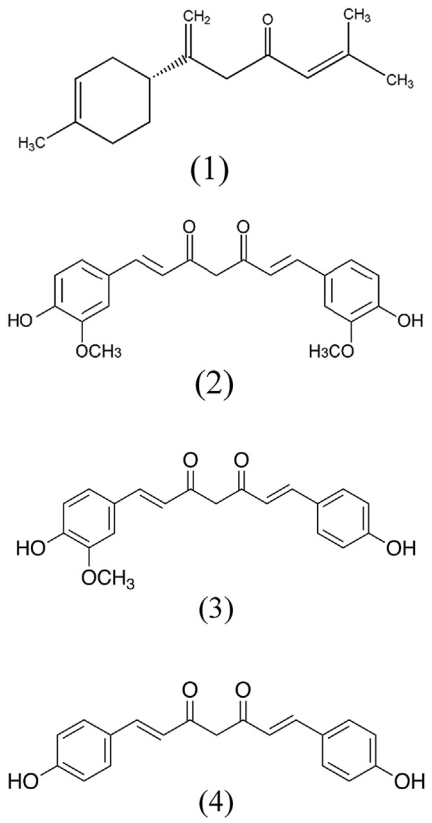

FIGURE 2.1 Chemical structure of xanthorrhizol (1), curcumin (2), demethoxycurcumin (3), bisdemethoxycurcumin (4).

1.2 Zingiber officinale

Ginger, scientifically known as *Zingiber officinale* Roscoe, belonging to family Zingiberaceae, is one of the most important plants with several medicinal, nutritional, and ethnomedical values, and hence explored extensively all over the world as a spice, flavoring agent, and herbal medicine [13].

Ginger originated in Southeast Asia. It has been cultivated for thousands of years as a spice as well as for medicinal purposes in countries like India, China, Nigeria, Indonesia, Bangladesh, Thailand, Philippines, and Jamaica. It is also grown in Australia, Fiji, Brazil, Sierra Leone, Japan, United Kingdom, United States, and Saudi Arabia. Ginger is an herbaceous rhizomatous perennial, reaching up to 90 cm in height under cultivation. It is widely used in a variety of foods because of its nutritional value and flavoring compounds. Ginger rhizomes are a rich source of carbohydrates, vitamins, minerals, and iron. Phytochemical analysis describes the content of ginger rhizome with a variety of pharmacological effects. *Z. officinale* is reported to

contain essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, saponins, steroids, terpenoids, and tannins as the major phytochemical groups [13,14]. Ginger possesses its characteristic organoleptic properties due to two classes of constituents: the odor and the flavor, determined by the constituents of its steam-volatile oil. The volatile oil consists mainly of the mono- and sesquiterpenes; camphene, β-phellandrene, curcumene, cineole, geranyl acetate, terphineol, terpenes, borneol, geraniol, limonene, β-elemene, zingiberol, linalool, α-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol, and α- Zingiberol are the principal aroma-contributing components of ginger rhizome [14] (Fig. 2.2).

1.3 *Silybum marianum* L

Silybum marianum (L.) Gaertn, whose common name is milk thistle, is an edible plant belonging to the Asteraceae family [15,16]. Milk thistle is a native of the Mediterranean region and has also spread to East Asia, Europe, Australia, and the Americas. Since the first century, milk thistle has been used medicinally [17–20]. Its flowers, leaves, and roots have been used in the European diet as vegetable, and its achene is used as a coffee. It is considered as a spinach substitute. In 1968, a flavonolignan complex in milk thistle fruit was identified and isolated. The major bioactive substituent present in the plant is the flavonoid complex silymarin, which is about 80% of the extract. This complex was found to be responsible for the medicinal effects of the silymarin complex and is made up of three parts: silibinin (also called silybin), silydianin, and silychristin. Silibinin is the most active of the three, and is largely responsible for the hepatoprotective benefits attributed to silymarin (Fig. 2.3).

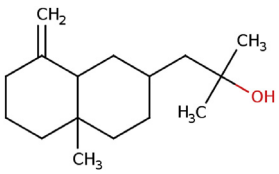

FIGURE 2.2 Chemical structure of zingiberol.

1.4 Gnetum gnemon

Gnetum gnemon L. (Gg) or melinjo is a plant growing abundantly in tropical areas such as Southeast Asia. This plant belongs to the genus of *Gnetum* (Gnetaceae family) [21,22]. The plant is a small- to medium-sized evergreen tree with nearly conical crown and a stature of 10–15 m. The stem is well branched and possesses a cylindrical bole and a diameter up to 40 cm. Leaves are petiolate, ovate-oblong, or elliptical, 10–20 cm long and 4–7 cm broad, reticulately veined, glabrous and shiny, dark green, apex acute to subacuminate, margins entire, base acute and phylotaxy opposite; young leaves are reddish purple. Inflorescences are borne on young shoots and older branches.

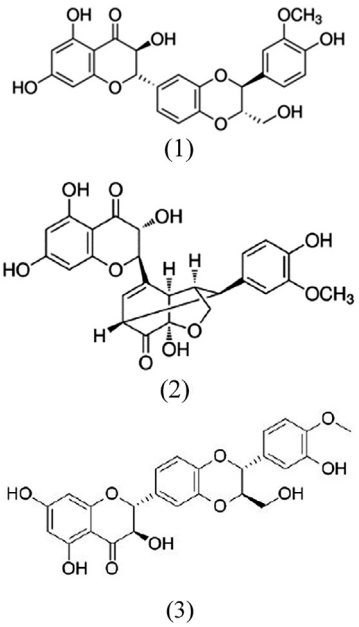

FIGURE 2.3 Chemical structure of silibinin (1), silydianin (2), and silychristin (3).

G. gnemon is one of the most studied wild plants. The plants from the family of Gnetaceae have been used as traditional medicines for many years. Several bioactive phytoconstituents present in *G. gnemon*, such as saponins, tannins, and Melinjo seeds contain abundant resveratrol (stilbenoid), mainly in the form of dimers (gnetin C). Gnetin C has been explored for more than 10 years, principally by Japanese scientists. Well-documented clinical data is already available and even more studies are continuing to emerge [21–24]. It has been reported that stilbenoids from melinjo showed strong antioxidant activity leading to various biological effects such as anti-inflammatory, antiaging, antihyperuricemia, antimicrobe, anticardiovascular, and anticancer [25] (Fig. 2.4).

1.5 Physalis angulata

Physalis angulata L. is an annual herb indigenous to tropical areas like Africa, Asia, and South America including the Amazon [26]. The plant grows up to 1 m high, plant parts are smooth and glabrescent, it bears small, yellow-colored flowers, and produces small, light yellowish- orange, edible fruit sometimes referred to as cape gooseberry or cut leaf ground cherry. Various phytochemicals including flavonoids, alkaloids, and plant steroids known as physalins (A and B), with anolides and secosteroids, which have never been reported before, are present in this plant [27–30]. *P. angulata* L. has been explored in recent clinical research, with preliminary evidence demonstrating it as an effective immune stimulant, toxic to numerous types of cancer like leukemia, and shown to have antimicrobial properties (Fig. 2.5).

2. Complexity of bioactive compounds

Most bioactive substances isolated from plants are either in the form of crude extract, fraction, and single compound show poor bioavailability, hence have low-therapeutic outcome, resulting from the challenging physicochemical properties, instability issues, or extensive in vivo response. Bioavailability and solubility are key issues that have emerged as top technical concerns in drug formulation and delivery even for bioactive compounds.

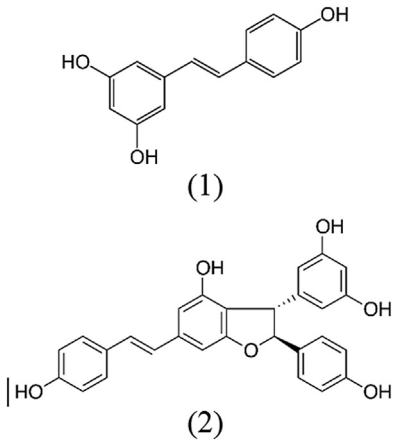

FIGURE 2.4 Chemical structure of resveratrol (1) and gnetin C (2).

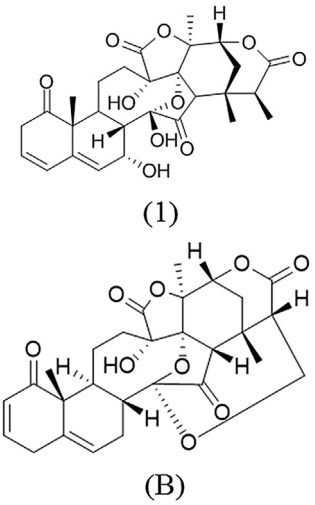

FIGURE 2.5 Chemical structure of physalin A (1) and physalin B (2).

In addition, stability of the active agents both physically and chemically also contribute significantly during formulation development. The main challenges faced by pharmaceutical companies in drug formulation as described in many reports [31–36] are safety (c.79%), appropriate therapeutic and delivery profiles (61%), and bioavailability (57%). In oral solid dosage forms, the top three formulation challenges are bioavailability (41%), stability (37%), and solubility (35%).

The fact that bioactive compounds are challenging during formulation and delivery has been described in several reports [31–36].

As discussed in the first part of introduction, several potential bioactive compounds exhibit a lack of pharmaceutical properties like low solubility and permeability, sensitivity toward external factors (humidity, light, and temperature), as well as presystemic degradation upon entering the body. All these challenges have led to unsuccessful therapy in the clinic using bioactive components.

3. Biological barriers

A major challenge in the drug delivery area is how to transport the active agents across the biological system entering the blood circulation and reaching the target of action to demonstrate the biological effects. Several biological barriers include the blood–brain barrier (BBB), the small intestine, nasal, skin, and the mucosa. Biological barriers are designed naturally with the aim to protect the organism from foreign materials that can damage homeostasis and physiologic function and eventually can threaten the organism's survival. Different types of biological barriers are described next to present the critical parameters on the therapeutic failures as well as to find the appropriate strategies or solutions by which a bioactive can be delivered successfully in vivo to exert desired clinical effects.

3.1 Physical barriers

For most therapeutics, reaching the targets of action require penetration across tissues and/or entry within cells. The design of strategies to control the transport of therapeutic compounds through these physiological barriers has become an imperative and a challenging need in the quest for better therapeutics. The physical barriers for drugs entering systemic circulation are the membrane, a biological architecture of a membrane border, like a single-layer or multilayer cell lining. This also includes lining of endothelial cells of blood vessels, stratum corneum of skin, lining of epithelial cells of various mucosa, BBB, blood ocular barrier, and the mucus covering the epithelial mucosa (Fig. 2.6).

3.2 Biochemical barriers

The biochemical barriers that can reduce the therapeutic function of a drug are the metabolizing enzymes, transporters, and efflux pumps. Drug-metabolizing enzymes are present in almost all parts of the body where the drug is passing through, such as gastrointestinal tract, respiratory system, ocular mucosa, in the blood circulation, and other entry points of drugs to the systemic compartment.

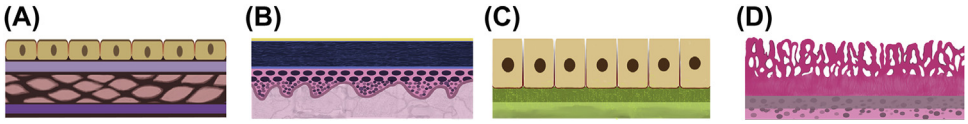

FIGURE 2.6 The physical barrier illustration of drug absorption: (A) lining endothelial cells, (B) stratum corneum, (C) lining epithelial cells, (D) mucosal membrane.

Drug transporters are the proteins that are present in many organs (liver, lung, kidney, intestine, brain, skin, blood vessels, and others). Naturally, the proteins play important roles for traffic between organs and elimination of drugs and foreign compounds. Their function somehow is beneficial, but they may also display deleterious effects that do not allow drugs to enter the target organ to show their effects. In the BBB, drug transporters and drug metabolizing enzymes are also present to control the access to the brain and local concentration of endobiotics and xenobiotics.

Efflux pumps demonstrate resistance to cytotoxic drugs, hence also act as a barrier for drug delivery. By their nature, efflux pumps are transport proteins involved in the extrusion of toxic substrates from cells into the external environment. These membrane proteins function as a pump that can decrease the intracellular accumulation of drug, leading to the ineffective drug therapy. For better drug delivery, the key to understanding how these pumps operate involves the determination of the structures of representative pumps and the elucidation of the conformational changes that accompany drug translocation.

4. Nanocarrier: a strategy to overcome biological barriers

A primary reason for drug failing to demonstrate its effect is the biology underlying the molecular-, cellular-, and tissue-level barriers, which makes the delivery process extremely complex. Therefore, to bypass the limitations regarding the biology of conventional drug delivery, it might be best to improve on the concepts and approaches that are efficient and effective [37,38].

One way to overcome barrier challenges could be formation of effective drug delivery. Nanoparticles, due to their smaller size and various other properties like surface coating, type of matrix used, and timely delivery, can help to deliver a drug at a target site. The successful outcome of the nanocarrier to help the bioactive compounds show their effect upon reaching the target site of action is also determined by the in vivo behavior of the nanocarrier, in particular in the phase of biological membrane passage to reach the systemic circulation, during traveling in the circulation to reach the target site and after reaching the target.

Various nanoparticles are being studied for delivery of synthetic as well as bioactive drugs. In this section, different drug delivery systems explored for bioactive drug delivery are discussed (Table 2.1).

Different types of nanocarrier systems are developed based on the characteristic of the bioactive compounds as well as the aim of their delivery target. Table 2.2 presents various nanosystems along with their method of preparation.

4.1 Lipid-based nanocarrier systems

Considering the complex in vivo barrier system in which the drugs are protected to be able to survive for therapeutic presentation, various strategies in the area of formulation and delivery either to target the drug at specific site or to control the drug release have recently been reported and described [31–36]. The former focuses more on the use of the excipients, the composition, and the manufacturing process, while the later emphasizes the drug-carrier constructs. The following discussion reviews the typically used drug delivery systems in bioactive delivery that are effective in overcoming the biological barriers, thereby improving the drug therapeutic index. In this category, we selected liposomes, nanoemulsions, and lipid nanoparticles; other forms of nanoparticles are still under research and have not yet reached the market like the above ones, hence we decided to discuss only the relevant ones.

TABLE 2.1 Bioactive-loaded nanocarrier systems and the potential medical promise.

Class	Category	Compound	Desired functionality	Challenges in formulation	Added value of nanoemulsions
Flavonoid	Flavanols	EGCG, catechin, epicatechin	Free-radical scavenging, anticancer, decreasing cholesterol level in blood, preventing arterial sclerosis, thrombosis, heart attacks, reducing fat and sugar uptake	Catechins generally exhibit high water solubility. Partition in the lipophilic core is improved by adding 1-dodecanol	- Increased storage stability of easily degradable catechins
	Flavonols	Quercetin, kaempferol, myricetin	Free-radical scavenging, fighting the effects of aging and inflammation, downregulating or suppressing inflammatory pathways and functions	The scarce solubility of most flavonols in oil phase requires the addition of amphiphilic molecules in the lipophilic core	- Improved thermo- and photostability - Enhanced delivery
	Flavones	Apigenin, luteolin, rutin, tangeretin	Antimutagenic, antiinvasive, and antiproliferative agent	Supersaturated flavones in oil phases easily form crystals, requiring the addition of compounds, such as soy protein isolates, to slow down the crystallization process	- Improved physical stability - Bioaccessibility
	Flavanones	Naringenin, hesperidin	Antiinflammatory, anticarcinogenic, hepatoprotective, and antilipid peroxidation	Flavanones exhibit poor water solubility. Oil and emulsifier are added to ensure maximum loading and stability in the nanoemulsion	- Increased release of compounds - Improved the bioavailability
	Isoflavones	Daidzein, genistein, puerarin	Protection against hormone-related disorders, menopausal symptoms, heart disease, and osteoporosis	Incorporation in oil droplets should be promoted by suitable emulsifiers (i.e., lecithin)	Improved the permeation through epidermal layers
Nonflavonoids	Hydroxybenzoic acids	Gallic acid, ellagic acid, *p*-hydroxybenzoic acid	Antiproliferative and antioxidant	Complexation with phospholipids is required to increase physical stability in nanoemulsions	Increased bioaccessibility, reduced interaction with the food matrix
	Hydroxycinnamic acids	Cinnamic acid, coumaric acid, ferulic acid, caffeic acid	Free-radical scavenging, preventing cell damage by ultraviolet light, antiaging, decreasing blood glucose	The solubility of some phenolic acids is very low in aqueous solutions, but they can easily be adsorbed at oil/water interface of nanoemulsions	Improved biological activity, permeability, the absence of cytotoxic effect

(*Continued*)

TABLE 2.1 Bioactive-loaded nanocarrier systems and the potential medical promise.—cont'd

Class	Category	Compound	Desired functionality	Challenges in formulation	Added value of nanoemulsions
	Stilbenes	Trans-resveratrol	Anticancer, antiinflammation, lowering low-density lipoproteins (bad cholesterol), fighting the plaque buildup leading to Alzheimer disease, preventing insulin resistance	Poor solubility in water and in oil requires either high amounts of surfactants or a combination of lipophilic and hydrophilic emulsifiers	- Improved IV-light stability - Enhanced cell permeation
	Curcuminoids	Curcumin	Antiinflammatory, antioxidant, boosting brain-derived neurotrophic factor, lowering the risk of heart disease, anticancer, fighting age-related chronic disease	Poor solubility in water and in oil requires the use of amphiphilic molecules such as lecithin in the lipid phase	- Improved cell uptake and anticancer activity - Enhanced food compatibility and reduced impact on sensory properties
Carotenoids	Carotenes	β-Carotene, lycopene	Antioxidant, free-radical scavenging, decreasing the risk of cardiovascular disease, oral cavity, and lung cancers	Light and oxidative instability requires the use of biopolymers in nanoemulsions formulation	Improved physical stability, control of lipolysis, and release
	Xanthophylls	Lutein, zeaxanthin	Preventing macular degeneration, promoting normal visual functions, strengthening eye tissue, supporting visual acuity and brain function	Limited solubility and dissolution requires complex formulation	Improved bioavailability

Among various nanocarriers developed to transport the active substances, liposomes, lipid-based nanocarriers, and nanoemulsions are more promising because of their diversity, favorable biocompatibility, and specific functionality.

In the case of lipid nanoparticles, a majority of lipids excipients are derived from dietary oils/fats, which offers advantages in terms of biodegradability and the ability to penetrate the biological membrane barriers. The selection of lipid by considering the chemical structure and properties determines the type of nanocarriers (e.g., solid lipid nanoparticle, nano/microemulsion, SEDDS/SMEDDS/SNEDDS, nanocapsule, liposome), the power of the carrier to load the active substance, and the capability to improve the drug therapeutic index. Therefore, types of lipid are very important for successful delivery of the bioactive compounds loaded in the nanocarrier systems.

4.1.1 Liposomes

Liposomes are tiny bilayer vesicles with spherical shape that can be formed from cholesterol and/or natural inert phospholipids.

TABLE 2.2 Various nanosystems for effective bioactive compound delivery.

Nanosystem	Technique	Composition	Bioactive compound	Size (nm)	References
Nanocapsules	Ionic pregelation/ coacervation	Chitosan, alginate	Naringenin	200–300	[39]
	Ionotropic polyelectrolyte pregelation	Alginate/chitosan/pluronic	Curcumin	100–120	[40]
	Ionotropic polyelectrolyte pregelation	Alginate/chitosan	Vitamin B2	86–200	[41]
Nanohydrogels	Physical self-assembly	β-lactoglobulin and low methoxyl pectin	ω-3 fatty acids	100	[42]
	Temperature- and pH-induced gelation	β-lactoglobulin	Epigallocate-chin-3-gallate	7–10	[43]
	Temperature-induced gelation	β-Lactoglobulin/hen egg white protein/alginate	α-Tocopherol	–	[44]
	Temperature-induced gelation	β-lactoglobulin	Curcumin	142	[45]
Nanoemulsions	High-pressure homogenization	Corn oil, Tween 20, SDS, and DTAB	Curcumin	119.5–152.9	[46]
	Solvent displacement + ultraturrax	Hexane, Tween 20	β-carotene	9–280	[47]
	Melt-homogenization	Medium-chain triglycerides, trimyristin, and tristearin	Curcumin	130–205	[48]
Solid lipid nanoparticles	Microemulsification	Polysorbate 80/soy lecithin	Curcumin	134.6	[49]
	High-pressure homogenization	Soy lecithin/sodium glycocholate/glycerol	Curcumin	100–110	[50]
Micelles	Self-assembly	Casein	β-Carotene	80	[51]
		β-casein	Curcumin	–	[52]

The bilayers consist of hydrophobic and hydrophilic compartments that enable a wide range of drugs to encapsulate, hence are a promising system for drug delivery. The type of lipids composing liposomes determine the surface charge, size, and the method of liposome preparation. The surface rigidity and fluidity of liposomes are influenced using additional agents like cholesterol. The choice of liposome preparation method is dependent on a variety of factors like lipid composition and size for in vivo drug delivery, etc.

Liposomes have demonstrated the potential benefit to improve the bioactivity of various natural compounds with lack in pharmaceutical properties [74]. Bonechi et al. described the improved therapeutics of various plant-derived phenolic compounds after they were incorporated into liposomes [75]. As the natural compounds are appreciated for their broad spectrum activities, this makes them more appropriate to interfere in multifactorial diseases, such as cancer. As compared to synthetic compounds, natural bioactive compounds

generally have better safety profiles, and are well accepted by the public. Despite these factors, the use of bioactive compounds poses a number of challenges that need to be overcome for better establishment as clinically effective therapeutic agents.

Currently, there is a huge lack of human clinical trials that address their absorption, distribution, metabolism, and excretion in relation to efficacy. As reported, various compounds that indicated poor bioavailability as well as being unstable and prone to degradation or oxidation, such as resveratrol (logP 3.4), thymol (logP 3.4), caffeic acid (logP 1.5), caffeic acid phenethyl ester (logP 3.9), carvacol (logP 3.4), and carvacrol disodiumphosphate (logP −2.0), have been successfully formulated into liposomal systems, resulting in better properties for each compound [75].

In line with the reports of Coimbra et al., Bonechi et al. [75] described liposome formulations made by a saturated phosphatidyl-choline (DPPC) and cholesterol (or its positively charged derivative, DC-CHOL) to optimize the loading of a rigid hydrophobic molecule such as resveratrol. They demonstrated the safe use of the systems on stabilized cell lines (mouse fibroblast NIH-3T3 and human astrocytes U373-MG).

Recent reports by Cavalcanti et al. [76] describe the successful liposomal formulation on new compounds of natural origin that exhibit antimicrobial activity: usnic acid (UA), a secondary lichen metabolite; and β-lapachone (β-lap), a naphthoquinone derived from lapachol extracted from Tabebuia avellanedae bark. These molecules exhibit proven antimicrobial activity, however, show low water solubility and high toxicity. Liposomes containing β-lap (β-lap-lipo) or usnic acid (UA-lipo) were prepared by the thin lipid film hydration method followed by sonication and were able to improve the antimicrobial activity of vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus*.

The role of TPGS-coated resveratrol liposomes (RSV-TPGS-Lipo) was investigated by Vijayakumar et al. to improve pharmacokinetic parameters and brain-targeted delivery of RSV after intravenous (i.v.) administration in rats. They also studied passive brain targeting efficacy and hemocompatibility of RSV-TPGS-Lipo for revealing their potential and safe i.v. administration for treatment of glioma. In vitro study demonstrated that RSVTPGS-Lipo 2 showed higher cytotoxicity due to presence of TPGS, which is known for its cytotoxic potential. The liposomes were highly concentrated in the cytoplasm of the cells, which is a major site of action of RSV for its anticancer activity. This finding confirms the promise of liposomal approach to encapsulate a potential natural anticancer compound with high cell selectivity [77].

4.1.2 *Nanoemulsions*

Among lipid-based nanocarrier systems, the nanoemulsion is most commonly used system for delivery of various bioactive compounds. This is because of its easy preparation at both laboratory and industry production scale, and the unique emulsion characteristics compared to other nanocarrier systems. The flexibilities of nanoemulsions are promising to create novel carrier systems with advanced potential benefits as drug transporters.

Nanoemulsions can also be used as building blocks for other types of structures, such as filled hydrogels. Filled hydrogels are designed to encapsulate, protect, and control the release of bioactive components by changing their dimensions, internal composition, or structure. Colloidosomes or microclusters are other structures that can be derived from nanoemulsions. A colloidosome consists of a large central particle with smaller particles adsorbed to its surface, whereas a microcluster consists of a number of smaller particles held together by attractive forces. These structures are created from nanoemulsions in order to alter the rheological, optical,

or stability properties of materials or for controlled-release applications as well.

A very recent study reported the potential use of nanoemulsion for thymol, an essential oil component of plants, and Quillaja saponin, a glycoside surfactant of the Quillaja tree [78]. Thymol(2-isopropyl-5-methylphenol), a major essential oil component of plants from the Lamiaceae family, possesses the phenolic hydroxyl group that contributes to its antimicrobial activity. Thymol has been classified as a generally recognized as safe (GRAS) by the U.S Food and Drug Administration in its use as a food additive. Its application has been widely reported in the medical, food, and agricultural fields. However, like other compounds, the main challenge is low water solubility, which limits its application in aqueous medium, as well as being unstable physically and chemically in the presence of oxygen, light, and temperature. All of these things eventually limit its biological activity and its efficiency.

Kumari et al. reported thymol nanoemulsion prepared by sonication method is able to improve the antibacterial effect of the thymol against bacterial pustule disease and growth promoting action on soybean [78]. The 50-min sonication of mixture of thymol and saponin in the ratio of 6:1 (w/v) in deionized water resulted in nanoglobules with the size of about 250 nm. The nanoemulsion with concentration of 0.01% −0.06% inhibited the growth of *Xanthomonas axonopodis.* In addition, the nanoemulsion of thymol also lowered the disease severity and increased percent efficacy of disease control of bacterial pustule in soybean caused by *X. axonopodis* pv *glycine.*

Other reports described the benefit of lipid-based nanocarrier, i.e., nanoemulsion and nanostructured lipid carriers (NLCs) to improve solubility as well as the stability of lutein against UV light [79]. Lutein, a natural carotenoid, has strong antioxidant property, which can protect skin from the damage due to photo irradiation. The lutein-loaded nanocarriers prepared with high-pressure homogenization have the mean particle size of about 150 nm to maximum 350 nm. The penetration study in in vitro system using cellulose membrane demonstrated that lutein loaded in nanoemulsion passed the membrane with highest percentage of 60% after 24 h, as compared to NLCs. Permeation study using fresh pig ear skin showed no or very little lutein loaded in NLCs was absorbed to systemic circulation.

Another potential promise of nanoemulsion as bioactive carrier was demonstrated by Shofia et al. on brown seaweed against colon cancer cell lines HCT 116 [80]. For centuries, seaweeds have been used as a food throughout Asia, and because of its high nutrient content seaweeds are of high pharmaceutical interest. Polysaccharides from brown seaweeds have been reported to have potent bioactive functions like antiinflammatory activity, antioxidant activity, and antiproliferative effect on various cancer cells. Nanoemulsions and NLCs were developed to overcome the instability and bioavailability problem of exopolysaccharides extracted from brown seaweed (*Sargassum longifolium*). Nanoemulsions were prepared using essential oil (orange oil) and biosurfactants (Span 80 and Pluronic L81) by high shear stirring followed by ultrasonication method at room temperature. Combination of two different surfactants aimed to maintain the synergistic effect on emulsion stability.

In other work, encapsulation of curcumin into nanoemulsion system was established using low- and high-energy techniques [81—83]. Incorporation of curcumin, a phenolic substance present in *Curcuma* sp, improved the pharmaceutics property as well as the chemical stability of this yellow compound leading to a more flexible formulation development. Some reports regarding the use of nanoemulsion for bioactive delivery are also presented in Tables 2.2 and 2.3.

TABLE 2.3 The materials-forming nanosystem for bioactive compound encapsulation.

Encapsulated nutrient	Type of delivery system	Main ingredients	References
Vitamin B2	Nanoparticle	Alginate and chitosan	[41]
Vitamin D3	Nanoparticle	Carboxymethyl chitosan and soy protein	[53]
Rutin	Nanocomplex	Sodium caseinate and pectin	[54]
EPA/DHA	Nanoparticle	Sodium caseinate and gum arabic	[55]
Poly-L-lysine	LbL nanocapsule	Chitosan and fucoidan	[56]
Glycomacropeptide	LbL nanocapsule	Chitosan and alginate	[57]
Quercetin	SLN-nanostructured lipid carriers/ lipid nanoemulsions (LNE)	MCT as oil phase, Tween 80, lecithin and span 20 as emulsifiers	[58]
Quercetin	Nanoparticle	Chitosan and lecithin	[59]
Curcumin	Nanoemulsions	MCT as oil phase and WPC and Tween 80 as emulsifiers	[60]
β-Carotene	Micelle	Casein	[51]
β-Carotene	Nanoemulsions	Tween 20	[47,61]
Resveratrol	Multilamellar liposome	Lecithin	[62]
Curcumin	Interpenetrating polymeric network nanogel	Gelatin	[63]
Curcumin	Core-shell biopolymer nanoparticle	Zein (core) and pectin (shell)	[64]
Chlorogenic acid	Nanoparticle	Chitosan	[65]
Folic acid	Nanocomplex	β-Lactoglobulin and sodium alginate	[66]
Resveratrol, rutin, hesperidin, hesperetin, curcumin, quercetin, apigenin	Nanosuspensions and smart crystals	Hydrophilic surfactants	[67–73]

4.1.3 *Solid lipid nanoparticles*

Solid lipid nanoparticles (SLNs) were first described in 1991, as an alternative carrier structure to previously developed colloidal carriers such as emulsions, liposomes, and micelle. SLN is a colloidal nanocarrier with size in the range of 50–1000 nm composed by lipid. Like other lipid-based carrier systems, SLNs offer potential benefit to improve the bioavailability of bioactive compounds through various mechanisms including enhanced solubility, permeability across biological membrane, protection of the labile molecules against external factors, as well as modification of the release of the active molecules.

Various bioactive compounds loaded in SLNs show better performance as compared to their free form, such as lutein, rutin, curcumin, Q10, and others as shown in Table 2.4 [67–73,79].

A recent report describes the development of Hibiscus rosa-sinensis extract loaded in SLNs using glycerol monostearate or beeswax as lipids

for antidepressants. The SLNs were prepared with emulsion-quenching technique resulting in nanoparticles of ~175 nm with better antidepressant activity in vivo as compared to native crude extract [84]. SLNs have higher physicochemical stability and protect the labile drugs from degradation. In addition, the production could be done on large scale, which makes this nanocarrier system more attractive as compared to other lipid-based systems. Other benefits of SLNs are that the matrix is solid, which protects the drug from chemical degradation, and the crystallization of product causes efficient encapsulation and release of drugs, enabling use of SLNs for various routes of administration.

Table 2.4 summarizes the studies demonstrating the potential benefits of various bioactive molecules loaded on SLNs/NLCs using different techniques of preparation.

5. Safe-by-design bioactive-loaded nanocarrier system development

Safe-by-design is a concept that is well established in fields like building, nuclear technology, water treatment, health facilities, and occupational health and safety. It describes safety measures for the prevention of accidents, illnesses, or environmental damage that are applied during the design stage of a facility, process, practice, material, or product. Application of this concept requires comprehensive knowledge questioning of what properties make a nanomaterial or nanoproduct safe. Nanomaterials are distinguished by their physical properties such as optic, magnetic, electric, mechanic, solubility, and others, which are better compared to those of the materials formed. The mechanisms of occurrence of nanotoxicity may be the result of various factors: the composition, the particle size and shape, solubility, ability for aggregation, surface reactivity and production of reactive oxygen species, as well as the route of administration. The first is most important when the nanocarrier system will be developed. The choice of GRAS excipients at least will minimize risk use of the nanoconstruct for human health.

Safety consideration is made not only focusing on humans but also on the environment. Several studies must be performed prior to human application ranging from in vitro toxicity tests to in vivo acute, subchronic, and chronic evaluations. As we previously reported, nanoemulsion composed from castor oil, Cremophor RH 40, and PEG 400 is safe upon incubation on various types of cell line as well as orally administered to Webster mice [94]. The nanoemulsion was successfully used to carry potent phytochemicals such as curcumin [81–83] for various studies both in vitro and in vivo.

The reports on safety data of several bioactive compounds loaded in various types of nanocarrier system are presented in Table 2.5.

6. Cellular uptake capability of bioactive-loaded nanocarrier system

There are two main mechanisms of transport that affect nanoparticles: transcellular and paracellular routes [102]. Transcellular transport is a process by which the cells of a tissue utilize a mechanism of transport through the cell [102,103], whereas paracellular transport is a process that occurs due to free passage or physical effect that passes through extracellular spaces [104].

Although these mechanisms are common to many molecules, their role in nanoparticle uptake is lesser known [105]. Nanomaterials may enter cells and be readily transported through a number of different mechanisms, including endocytosis, active transport, and facilitated diffusion [106–108]. The potential of a nanoparticle to be transported through any one of these mechanisms is inherently and primarily influenced by size, surface charge, and reactivity [109]. Positively charged nanomaterials will capitalize on the negatively charged tight junction filaments between cells, increasing

TABLE 2.4 The advantages of lipid nanoparticles (SLNs/NLCs) to improve different bioactive molecules.

Bioactives	Formulation/preparation	Production method	Route	Advantages	References
D-limonene	Palm oil soy lecithin hot	HPH	Oral/food	• Increased antimicrobial activity	[85]
Curcumin	Hydrogenated soya phosphatidylcholine, distearoyl, phosphatidylethanolamine, cholesterol, and triolein	HPH	Oral	• Increased cellular uptake and • Reduced cytotoxicity	[86]
Vitamin A	Glyceryl bebenate	Ultraturax	Transdermal delivery	• Increased skin permeation • Improved release rate	[87]
Lutein	Solid lipid or mixture of solid and liquid	HPH	Topical delivery	• Increased drug stability against UV • Controls drug release to the skin • Better permeability	[79]
Leonotis leonurus	TagoCare, Cutina CP, Miglyol	HPH	Oral	• Increased bioavailability	[88]
Rosmarinic acid	Witepsol-Carnauba wax	Ultrasonication	Oral	• Increased stability against gastrointestinal degradation • Improved drug delivery	[89]
Cryptotanshinone	Glyceril monostearate – soy lecithin	Sonication-HPH	Oral	• Bioavailability Enhancement	[90]
Astaxanthin	Oleic acid, Glyceryl behenate, Tween-80, Lecithin	Melt emulsification-sonication	Oral	• Improved physical stability	[91]
Green tea extract	Cetyl palmitate, Glyceryl stearate, vegetable oil, Tween-20/80	Modified HPH	Oral	• Improved antioxidant activity • Increased antimicrobial activity	[92]
Lycopene	Eumulgin SG, orange wax, rice bran oil	HPH	Oral	• Enhanced chemical stability • Improved antioxidant activity	[93]

their transport through paracellular mechanisms [110]. Various nano-based approaches have been applied to enhance the uptake of drugs with poor bioavailability or aqueous solubility [111,112]. The nanomaterials are readily transported via highly specific cellular mechanisms, such as clathrin-mediated endocytosis in the oral mucosa [105].

Lu et al. described the correlation between nanoemulsion structure and cellular uptake of encapsulated β-carotene in vitro using $CaCo_2$ cells [113]. The aim of nanoencapsulation of the

TABLE 2.5 Bioactive-loaded nanocarrier systems and the safety confirmation data.

Materials and Methods	Model used	Size (nm)	Dose tested	Assay	Cytotoxicity results	References
In vitro studies						
SLN						
Curcumin/trimyristin and emulsifiers soy lecithin, sodium glycocholate and poloxamer 407 (high-pressure homogenization)	Caco-2 and HT29-MTX cells (75:25)	100 ± 10	3.125 μg/mL, 2 h	NADPH production using a colorimetric assap (CellTiter 96)	No cytotoxic effect neither on Caco-2 nor on HT29-MTX	[50]
β-Carotene (BC)/SC, WPI, SPI) (homogenization-evaporation)	Caco-2 cells	75 (SC)/90 (SPI)	10 mg BC/mL, 10 times diluted or more, 48 h	MTT	Low toxicity at about 10 mg BC/mL (73%–92% of CV) and insignificant when diluted 1 time or more (CV > 95%)	[95]
Nanoliposomes						
Lactoferrin/PC/cholesterol/Tween 80 (reverse-phase evaporation)	Caco-2	<100	1, 5, and 10 mg/mL	MTT, ROS detection, and apoptosis induction (AO/EB staining); LDH	Mitochondrial activity reduction; CV decreased (at 5 and 10 mg/mL); ROS increased (5 mg/mL)	[96]
Nanoemulsions						
Resveratrol/soy lecithin/GMO/sugar ester mixture/peanut oil/polysorbate Tween 20 (high-pressure homogenization)	Caco-2 cells	128–235	Nanoemulsion dilution (1:10, 1:50 and 1:100), 24, 28, and 72 h	XTT assay and confocal laser scanning microscopy	Formulations do not cause any harm to the cells	[97]
Curcumin/β-lactoglobulin complexes emulsifier WPI (freeze-drying of nanoemulsion)	Caco-2 cells	50–200	20–400 μg/mL, 24 h	MTT	Curcumin concentrations were not toxic to the cells at 100 μg/mL	[98]
Polymer and SLN						
GLP-1/PLGA, Witepsol E85 lipid and porous silicon (Psi)/chitosan coated (solvent emulsification-evaporation method)	Caco-2 and HT29-MTX cells	200	1.5, 3.75, 0.5 and 15 μg mL, 3 and 12 h	CellTiter-Glo luminescence assay	CV above 80%, with HT29-MTX cells, the nanoparticles showed less toxicity compared to Caco-2 cells at the same point	[99]
Rosmarinic acid (RA)	Lymphocyte cell	900	0.15 mg/mL	MTT	The SLN is safe when loaded with moderate concentrations of RA, without in vitro genotoxicity	[89]
Peptide-polysaccharide nanoparticles						
Epigallocatechin-3-gallate/genipin-crosslinked caseinophosphopeptide-chitosan (CPP-CS)	Human gastric BGC823 cells	<300	12.5–200 μg/mL, 24, 36 and 48 h	Trypan blue dye exclusion test	Naked CPP-CS NPs cross-linked with genipin did not show cytotoxicity	[100]
In vivo studies						
Hydrogel nanoparticles						
Curcumin/HPMC/PVP (solvent emulsion-evaporation technique and free-drying)	Holtzman rats	100	2000 mg/kg, 14 days	Acute and subacute toxicity	No toxicity	[101]

bioactive β-carotene was to improve the cellular uptake of the compound. Enhanced cellular uptake is also considered as one of the potential mechanisms of improved bioavailability of bioactive nutrients, because uptake of nanoparticles by digestive tract mucosa via mucosa-associated lymphatic tissues is possible. Nanoencapsulation in an emulsion that can also significantly improve the cellular uptake of encapsulated molecules. These important findings demonstrated that cellular uptake of encapsulated BC is dependent on particle size and interfacial structure (emulsifiers).

The influence of surfactants such as Tween 80, sodium dodecyl sulfate, and sodium caseinate on physicochemical, morphological, and cellular uptake properties of lutein nanodispersions was reported by Tan et al. [114]. The surfactants used for that study showed different stabilizing mechanisms on lutein nanodispersions. The lutein nanodispersions in this study were produced using the solvent displacement method and displayed good physicochemical properties. Their interesting findings demonstrated how the different types of surfactants could affect the characteristics of the lutein nanodispersions produced. As well, the utilization of a small-molecule electrostatic surfactant, such as sodium dodecyl sulfate, could be useful in producing lutein nanodispersions with small particle sizes (of less than 100 nm) and high zeta potential values.

7. Surface modification of nanocarriers

Nanocarriers for drug delivery systems offer advantages that are desirable for therapeutics. Drug nanocarriers also have the ability to improve the pharmacokinetics and increase biodistribution of therapeutic agents at the target organs that result in improved efficacy and reduction of adverse effects. The nanocarriers have been engineered to target difficult-to-treat diseases like tumors and disease sites that have permeable vasculature, allowing easy delivery of payload. Specific targeting and reduced clearance increases the therapeutic index, which consequently lowers the dose required for efficacy.

Nanodrug carriers can increase the bioavailability of the drug, including natural drugs at the target site, reduce the frequency of administration, and reach sites that are otherwise inaccessible. In order to be useful in drug delivery, the nanocarrier must possess very important characteristics. Functionalization or surface modification of the bioactive-loaded nanomaterials is often done to obtain unique and specific properties in the biological system, i.e., long systemic circulation, organ or cell selectivity to improve their efficacy and lower the adverse effects.

The first attempt at developing modified nanocarrier for active drug targeting was proposed in the 19th century by the scientist Paul Elrich. Since then, more attempts were done to improve the therapeutic value of the nanocarrier, which also helps to load bioactive compounds as presented in Table 2.6.

Other promising modification was also demonstrated by SLNs [115]. The conventional SLNs have several advantages, although there is a challenge to oral delivery of bioactive compounds such as burst release of the loaded compounds in the stomach at a lower pH of about 1−3. To solve this matter, SLNs are subjected to surface modification to improve the therapeutic benefit. Surface-modified SLNs can be constructed using heparin, albumin, polyethylene glycol, and polysaccharides. Chitosan is also used as it is highly degradable and has lower immunogenicity, thus it is suitable for controlled oral delivery of the bioactive compounds under various pH conditions.

TABLE 2.6 Surface modification-functionalization of nanocarrier to improve the nanosystem properties.

Carrier system	Surface modification	Bioactive compound	Benefit	References
Nanoemulsion				
Solid lipid nanoparticle	N-carboxymethyl chitosan (NCC) coating	Curcumin	To inhibit the rapid release of curcumin in acidic environment and enhance the bioavailability	[116]
Solid lipid nanoparticle	Chitosan-coated	Resveratrol, caffeic acid, ferulic acid	To enhance the delivery	[117,118]
Solid lipid nanoparticle	Trimethyl chitosan-coated	Curcumin, resveratrol	To enhance the bioavailability	[117,119]
Solid lipid nanoparticle	N-trimethyl chitosan-g-palmitic acid	Resveratrol	To enhance the bioavailability	[120]
Liposome	PEGylated	Coenzyme Q10	Long-circulating liposomal delivery systems	[121]

8. Biokinetic profile of bioactive-loaded nanocarriers

The first step in demonstrating the efficacy of the bioactive-loaded nanocarrier when given through oral route is that it must pass through the gastrointestinal (GIT) barrier. After the ingestion process, there are some barriers to overcome before bioactive compounds can reach the systemic circulation in an active form. The bioavailability of these compounds can be impaired due to various physicochemical and physiological phenomena such as restricted liberation from delivery matrices, insufficient gastric residence time, low solubility in gastrointestinal fluids, formation of insoluble complexes with other components in the GIT, low permeability across the mucus layer or epithelium cells, and/or molecular transformations/chemical instability in the GIT.

These phenomena can cause a large percentage of compounds to remain unabsorbed and be excreted out of the body. Tables 2.7 and 2.8 present the in vivo bioaccessibility and bioavailability of different types of nanocarrier systems loading bioactive compounds.

9. Challenges of bioactive-loaded nanocarrier to clinical translation

The nanocarrier intended for clinical applications should use materials safe as pharmaceutical excipients and its formulation should have good manufacture processes with scale-up ability. The challenge is to design safe, approvable, and easily scaled-up production, intellectual property, government regulations, and overall cost-effectiveness in comparison to current therapies.

The design of bioactive-loaded nanocarrier systems must consider several aspects such as route of administration, complexity in formulation design, final dosage form for human use, biocompatibility and biodegradability, and pharmaceutical stability (physical and chemical). In addition, the pre- and clinical evaluations are also important. Considerations for preclinical evaluation include validation and standardization of assays for early detection of toxicity, evaluation in appropriate animal models of disease, and adequate understanding of in vivo behavior such as cellular and molecular interactions, pharmacokinetic profile, and the pharmacodynamics

TABLE 2.7 Various bioactive-loaded nanocarrier systems and their bioaccessibility.

Nutrient	Delivery system	Details	Composition/testing details	References
β-Carotene	Nanoemulsions	Encapsulation active	3.1% (dispersed in MCT)	[122]
			35.6% (nanoencapsulated)	
Lycopene	Nanoemulsions	Size	0.01% (Unemulsified)	[123]
			0.53% (size: 150 nm)	
			0.77% (size: 69 nm)	
Quercetin	SLM nanostructured lipid carrier (NLC), LNE	Lipid nanocarrier	39.7% (SLN)	[58]
			52.7% (NLC)	
			58.4% (LNE)	
β-Carotene	Nanoemulsions	Carrier oil	≈66% (LCT)	[124]
			≈2% (MCT)	
			≈0% (orange oil)	
Curcumin	Nanoemulsions	Surfactant	16.4% (Tween 20)	[56]
			17.7% (SDS)	
			1.2% (DTAB)	
Resveratrol	Biopolymer nanoparticles (BnPs) and complexes (BC)	Nanoencapsulation, nanocarrier	≈73% (BnP)	[125]
			≈70% (BC)	
			≈60% (free)	
Curcumin	Nanosuspension	Active + surfactant	99% active content 100−500 nm	[73]
Apigenin			99.5% active content 210−450 nm	[72]

of the bioactive compound loaded in the nanocarrier. Currently, many aspects are still under exploratory phase and need collaboration and willingness of different expert areas.

Clinical evaluation for commercialization demands simplification of the development pathways from invention to the market. To minimize time and expense, evaluation of safety/toxicity in humans both acute and chronic, the evaluation of therapeutic efficacy in patients, as well as the optimal clinical trial design are key essentials.

In addition, quality and constant supply of herbal extracts or raw material are equally important for bioactive components to reach market success (Table 2.9).

9.1 Patents on herbal nanoparticles for breast cancer

The interest in nanoproduct developments is also reflected by several patents: Liang et al. [139] developed nano-micelles, and Zale et al. [140] developed polymeric nanoparticles of vinca alkaloids (vindesine, vinorelbine vincristine and vinblastine) using PEG for anticancer applications. These preparations have good

TABLE 2.8 List of various bioactive-loaded nanocarrier systems and their bioavailability.

Compound	Formulation type	Animal model	Bioavailability	Dose	References
Folic acid	Zein nanoparticles	Rats	2-fold higher than the free form	1 mg/kg	[127]
α-Tocopherol	Nanoemulsion	Male Wistar rats, 210 ± 10 g	2.6-fold increase	30 mg/kg	[128]
Lycopene (lipophilic carotenoid)	Lipid-based solid dispersion (LBSD)	Pigs, female landrace, 13–15 kg	2.4-fold higher than the commercial product Lycovit (in gelatin beadlets)	50 mg	[129]
Lutein	PLGA nanoparticle	Male Fischer 344 rats, 238 g	Increased pharmacokinetic parameters, such as C_{max} (54.5-fold) and AUC (77.6-fold) than the free form	10 mg/kg	[130]
Lutein	Low-molecular-weight chitosan	Swiss albino mice, 25 ± 2 g	Postprandial lutein level in the plasma 54.5% higher than control	200 μm	[131]
Silymarin	Lipid nanoparticles	Beagle dogs (15 ± 2 kg)	Higher bioavailability than their lipolysate counterparts	8 mg/kg	[132]
Curcumin	Lauryl sulfated chitosan	SD rats, 220–250 g	48.79-fold more than free form	10 mg/kg	[133]
Curcumin	Phosphatidylcholine-maltodextrin-based hydrophilic lipopolysaccharide	Albino Wistar rats, 200–250 g	130-fold increase oral bioavailability	50 mg/kg	[134]
Diosgenin in wild yam (*Dioscorea villosa)*	Liquid crystal (glyceryl monooleate + b-cyclodextrin)	Male Wistar rats (200–250 g)	6.2-fold more than free form	2 mL/kg	[135]
Capsaicin	(PVP)/sodium cholate/ phospholipid mixed polymeric micelles	Male SD rats	2.42-fold more than free form	90 mg/kg	[136]
Apigenin	Supercritical antisolvent process	Male Sprague–Dawley rats (230–270 g)	Absolute bioavailability increased from 2.0% for free coarse powder to 6.9% for nanocrystal	50 mg/kg	[137]
Resveratrol	Solid nanoparticles	Wistar male rats	8-fold increase than suspension	20 mg/kg	[138]

Acquired with permission from Ref. Nallamuthu I, Khanum F, Fathima SJ, Patil MM, Anand T. Enhanced nutrient delivery through nanoencapsulation techniques: the current trend in food industry, Book: nutrient delivery, Elsevier September 2016, 619.

TABLE 2.9 Commercial nanoherbals in the market.

Product name	Company	Ingredient	Category/ Administration route
LycoVit	BASF, Germany	Carotenoid lycopene	Nutraceutical/oral
Taiji ring	Limited Hebei, China	Nano-selenium rich black tea	Food/oral
Nanotea	Shenzhen Become Industry & Trade Co., Ltd.	Extract tea, selenium	Food/oral food
Canola active oil	Shemenm Haifa, Israel	Phytosterols,	
Fortified fruit juice	High Vive.com., USA	Fortified vitamin, lycopene, theanine, and sun-active iron	Food/oral
Nanoceuticals Slim Shake	RBC Lifesciences, rving, USA	Assorted flavors	Nutritional food/oral
NanoSlim	NanoSlim, Canada	*Lagerstroemia speciosa* L., cha' de bugre extract, green coffee extract and thallus powder and corosolic acid	Nutritional food/oral
Oat Nutritional Drink	Toddler Health, Los Angeles, USA	Assorted flavors	Nutritional food/oral
"Tip-Top" Up Bread	Enfield, Australia	Tuna fish oil	Nutritional food/oral
NanoResveratrol	Life Enhancement, USA	Solid triglyceride, phosphatidylcholine delivery	Nutritional food/oral
Nutri-Nano CoQ-10 3.1x Softgels	Solgar, USA	CoQ10, natural oils	Cosmetic/dermal
NovaSOL capsule	Aquaniva Darmstadt, Germany	–	Nutritional food/oral
Spray for Life Vitamin Supplements	Health Plus International, Inc., USA	Vitamin	Nutraceutical/oral
"Daily boost"	Jamba Juice Hawaii, USA	Vitamin or bioactive components	Nutraceutical/oral
"Color emulsion"	Wild Flavors, Inc, USA	β-Carotenal, apo-carotenal, or paprika	Food/ora
"Nano-silver" (NS)	A-DO Global Col., Ltd, South Korea	Silver	Food/oral
Cutanova Cream Nano Repair Q10	Dr. Rimpler, Germany	Q10, polypeptide, hibiscus extract, ginger extract, ketosugar	Cosmetic/dermal
Intensive Serum NanoRepair Q10	Dr. Rimpler, Germany	Q10, polypeptide, mafane extract	Cosmetic/dermal
Cutanova Cream NanoVital Q10	Dr. Rimpler, Germany	Q10, TiO2, polypeptide, ursolic acid, oleanolic acid, sunflower seed extract	Cosmetic/dermal

stability, improved drug distribution, increased effectiveness, and decreased toxicity and have shown efficiency in the clinical treatment of breast cancer.

Ringas et al. [141] provided a method of treating breast cancer by administering phosphovalproic acid, phosphor-ibuprofen, phosphorsulindac or their pharmaceutically acceptable salt, together with bioavailability enhancers like cimetidine and curcumin in the form of solid lipid nanoparticles, liposomes, or polymer molecules. Another invention to watch is encapsulation a physiologically effective dose of triterpene glycoside or triterpene complex nanoparticles in liposomes or exosomes that exhibit preventive or therapeutic activity in breast cancer [142].

10. Conclusion

Bioactive compounds derived from various plants are promising therapeutic agents in the future due to safety concerns, being environmentally friendly, and the availability of plenty of resources. Despite the lack of pharmaceutical properties of most natural products, there is great interest in the application of new technology for better formulation and delivery. Different types of nanocarrier systems offer potential pockets to pack bioactive compounds that lack pharmaceutical properties such as low solubility, permeability, and stability—three main parameters determining therapeutic success. Specific structures of these nanosystems can be modified on their surface to obtain certain properties, such as for selective distribution and control release, to make them suitable carriers in bioactive delivery. By considering the target of therapy, an appropriate nanosystem can be developed using unique material forming nanosystem and manufacturing technology. As well, the initiation of clinical studies of these bioactive-loaded nanosystems provides optimism for better therapeutic outcomes, in particular, for difficult to treat diseases that require safe long-term therapy with low cost.

References

[1] Ata A. International conference on primary health care, declaration of Alma-Ata. WHO Chron 1978;32:428–30.

[2] Larsen K. Distribution patterns and diversity centres of Zingiberaceae in SE Asia. Biol Skr 2005;55:219–28.

[3] Sirirugsa P, Larsen K, Maknoi C. The genus *Curcuma* L. (Zingiberaceae): distribution and classification with reference to species diversity in Thailand. Gard Bull (Singap) 2007;59:203–20.

[4] Ramachandran C, Lollett IV, Escalon E, Quirin KW, Melnick SJ. Anticancer potential and mechanism of action of mango ginger (*Curcuma amada* Roxb.) supercritical CO_2 extract in human glioblastoma cells. J Evid Based Complement Altern Med 2015;20:109–19.

[5] Li Y, Shi X, Zhang J, Zhang X, Martin RCG, et al. Hepatic protection and anticancer activity of *Curcuma*: a potential chemo preventive strategy against hepatocellular carcinoma. Int J Oncol 2014;44:505–13.

[6] Sahu B, Kenwat R, Chandrakar S. Medicinal value of *Curcuma cassia* Roxb: an overview. UK J Pharma Biosci 2016;4:69–74.

[7] Shukla DP, Shah KP, Rawal RM, Jain NK. Anticancer and cytotoxic potential of turmeric (*Curcuma longa*), neem (*Azadirachta indica*), tulasi (*Ocimum sanctum*) and ginger (*Zingiber officinale*) extracts on HeLa cell line. Int J Life Sci Sci Res 2016;2:309–15.

[8] Bavarsad K, Riahi MM, Saadat S, Barreto G, Atkin SL, Sahebkar A. Protective effects of curcumin against ischemia-reperfusion injury in the liver. Pharmacol Res 2018;141:53–62.

[9] L Hadem K, Sharan RN, Kma L. Inhibitory potential of methanolic extracts of Aristolochia tagala and *Curcuma caesia* on hepatocellular carcinoma induced by diethylnitrosamine in BALB/c mice. J Carcinog 2014;13:7.

[10] Hong GW, Hong SL, Lee GS, Yaacob H, Malek SN, et al. Non-aqueous extracts of *Curcuma mangga* rhizomes induced cell death in human colorectal adenocarcinoma cell line (HT29) via induction of apoptosis and cell cycle arrest at G0/G1 phase. Asian Pac J Trop Med 2016;9:8–18.

[11] Sanatombi R, Sanatombi K. Nutritional value, phytochemical composition, and biological activities of edible *Curcuma* species: a review. Int J Food Prop 2017;20:S2668–87.

[12] Sun W, Wang S, Zhao W, Wu C, Guo S, Gao H, Tao H, Lu J, Wang Y, Chen X. Chemical constituents and biological research on plants in the genus *Curcuma*. Crit Rev Food Sci Nutr 2017;57:1451–523.
[13] Dhanik J, Arya N, Nand V. A review on *Zingiber officinale*. J Pharmacogn Phytochem 2017;6:174–84.
[14] Ali BH, Blunde G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. Food Chem Toxicol 2008;46: 409–20.
[15] Lee DY, Liu Y. Molecular structure and stereochemistry of silybin A, silybin B, isosilybin A and isosilybin B, isolated from *Silybum marianum* (milk thistle). J Nat Prod 2003;66:1171–4.
[16] Veres T, Tyr S. Milk thistle (*Silybum marianum* (L.) Gaertn.) as a weed in sustainable crop rotation. Res J Agric Sci 2012;44:118–22.
[17] Bhattacharya S. Phytotherapeutic properties of milk thistle seeds: an overview. J Adv Pharm Educ Res 2011;1:69–79.
[18] Corchete P. *Silybum marianum* (L.) Gaertn: the source of silymarin. Bioact Mol Med Plants 2008:123–48.
[19] Polyak SJ, Morishima C, Lohmann V, Pal S, Lee DY, et al. Identification of hepatoprotective flavonolignans from silymarin. Proc Natl Acad Sci USA 2010;107: 5995–9.
[20] Kato E, Tokunaga Y, Sakan F. Stilbenoids isolated from the seeds of melinjo (*Gnetum gnemon* L.) and their biological activity. J Agric Food Chem 2009;57: 2544–9.
[21] Siswoyo TA, Mardiana E, Lee OK, Hoshokawa K. Isolation and characterization of antioxidant protein fractions from melinjo (*Gnetum gnemon*) seeds. J Agric Food Chem 2011;59:5648–56.
[22] Haycraft CJ, Carmichael JS. Development of sterile ovules on bisexual cones of *Gnetum gnemon* (Gnetaceae). Am J Bot 2011;88:1326–30.
[23] A Parhusip NJ, Sitanggang BA. Antimicrobial activity of melinjo seed and peel extract (*Gnetum gnemon*) against selected pathogenic bacteria. Microbiol Indones 2011;5:103–12.
[24] Tatefuji T, Yanagihara M, Fukushima S, Hashimoto K. Safety assessment of melinjo (*Gnetum gnemon* L.) seed extract: acute and sub chronic toxicity studies. Food Chem Toxicol 2014;67:230–5.
[25] Atuna S, Arianingruma R, Masatake N. Some phenolic compounds from stem bark of melinjo (*Gnetum gnemon*) and their activity test as antioxidant and UV-B protection. Proc J S Chem-ITB-UKM 2007:1–4.
[26] Bastos GNT, Santos ARS, Ferreira VMM, R Costa AM, Bispo CI, A Silveira AJ, M Do Nascimento JL. Antinociceptive effect of the aqueous extract obtained from roots of Physalis angulata L. on mice. J Ethnopharmacol 2006;103:241–5.
[27] Ramachandra RL, Sambi RK, Subrahmanya SN, Teruo M, Ruka N. New physalins from *Physalis angulata* and *Physalis lancifolia*. Structure and reactions of physalins D, I, G and K. PhytoChemistry 1980;19: 1175–81.
[28] Chen CM, Chen Z, Hsich C, Zin W, Wen S. Withangulatin a new withanolide from *Physalis angulata* L. Heterocycles 1990;31:371–5.
[29] Basey K, Mcgaw BA, Woolley JG. Phygrine an alkaloid from Physalis species. PhytoChemistry 1992;31: 4173–6.
[30] Shingu K, Yahara S, Okabe H, Nohara T. Three new withanolides, physagulins E, F and G from *Physalis angulata* L. Chem Pharm Bull 1992;40. 2448–245.
[31] Patil BS, Jayaprakasha GK, Chidambara Murthy KN, Vikram A. Bioactive compounds: historical perspectives, opportunities, and challenges. J Agric Food Chem 2009;57:8142–60.
[32] Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 2005;81:230–42.
[33] Benito P, Miller D. Iron absorption and bioavailability: an updated review. Nutr Res 1998;18:581–603.
[34] Fernàndez-Garcìa E, Carvajal-Lérida I, Pérez-Gàlvez A. *In vitro* bioaccessibility assessment as a prediction tool of nutritional efficiency. Nutr Res 2009;29: 751–60.
[35] Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79:727–47.
[36] Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000;130:2073–85.
[37] Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Ther 2008;83:761–9.
[38] Park K. Facing the truth about nanotechnology in drug delivery. ACS Nano 2013;7:7442–7.
[39] Maity S, Mukhopadhyay P, Kundu PP, Chakraborti AS. Alginate coated chitosan core-shell nanoparticles for efficient oral delivery of naringenin in diabetic animals – an *in vitro* and *in vivo* approach. Carbohydr Polym 2017;170:124–32.
[40] Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells, nanomedicine: nanotechnology. Biol Med 2010;6:153–60.
[41] Azevedo MA, Bourbon AI, Vicente AA, Cerqueira MA. Alginate/chitosan nanoparticles for encapsulation and controlled release of vitamin B2. Int J Biol Macromol 2014;71:141–6.

[42] Zimet P, Livney YD. Beta-lactoglobulin and its nanocomplexes with pectin as vehicles for w-3 polyunsaturated fatty acids. Food Hydrocolloids 2009;23: 1120−6.
[43] Li B, Du W, Jin J, Du Q. Preservation of (−)-epigallocatechin-3-gallate antioxidant properties loaded in heat treated β-lactoglobulin nanoparticles. J Agric Food Chem 2012;60(13):3477−84.
[44] Somchue W, Sermsri W, Shiowatana J, Siripinyanond A. Encapsulation of α-tocopherol in proteinbased delivery particles. Food Res Int 2009; 42:909−14.
[45] Sneharani AH, Karakkat JV, Singh SA, A Rao AG. Interaction of curcumin with β-lactoglobulin-stability, spectroscopic analysis, and molecular modeling of the complex. J Agric Food Chem 2010; 58:11130−9.
[46] Pinheiro AC, Lad M, Silva HD, Coimbra MA, Boland M, Vicente AA. Unravelling the behavior of curcumin nanoemulsions during in vitro digestion: effect of the surface charge. Soft Matter 2013;9:3147−54.
[47] Silva HD, Cerqueira MA, S Souza BW, Ribeiro C, Avides MC, C Quintas MA, Coimbra JSR, Carneiro-da-Cunha MG, A Vicente A. Nanoemulsions of β-carotene using a high-energy emulsification−evaporation technique. J Food Eng 2011;102:130−5.
[48] Noack A, Hause G, Mäder K. Physicochemical characterization of curcuminoid-loaded solid lipid nanoparticles. Int J Pharm 2012;423:440−51.
[49] Kakkar V, Singh S, Singla D, Kaur IP. Exploring solid lipid nanoparticles to enhance the oral bioavailability of curcumin. Mol Nutr Food Res 2011;55:495−503.
[50] Guri A, Gulseren I, Corredig M. Utilization of solid lipid nanoparticles for enhanced delivery of curcumin in cocultures of HT29-MTX and Caco-2 cells. Food Funct 2013;4:1410−9.
[51] Sáiz-Abajo MJ, González-Ferrero C, Moreno-Ruiz A, Romo-Hualde A, González-Navarro CJ. Thermal protection of β-carotene in re-assembled casein micelles during different processing technologies applied in food industry. Food Chem 2013;138:1581−7.
[52] Esmaili M, Ghaffari SM, Moosavi-Movahedi Z, Atri MS, Sharifizadeh A, Farhadi M, Yousefi R, Chobert M, Haertlé T, Moosavi-Movahedi AA. Beta casein-micelle as a nano vehicle for solubility enhancement of curcumin; food industry application. LWT − Food Sci Technol (Lebensmittel-Wissenschaft −Technol) 2011;44:2166−72.
[53] Teng Z, Luo Y, Wang Q. Carboxymethyl chitosan-soy protein complex nanoparticles for the encapsulation and controlled release of vitamin D3. Food Chem 2013a;141:524−32.
[54] Luo Y, Pan K, Zhong Q. Casein/pectin nanocomplexes as potential oral delivery vehicles. Int J Pharm 2015a;486:59−68.
[55] Ilyasoglu H, El SN. Nanoencapsulation of EPA/DHA with sodium caseinate−gum Arabic complex and its usage in the enrichment of fruit juice. LWT − Food Sci Technol (Lebensmittel-Wissenschaft -Technol) 2014;56:461−8.
[56] Pinheiro AC, Bourbon AI, Cerqueira MA, Maricato E, Nunes C, Coimbra MA, Vicente AA. Chitosan/fucoidan multilayer nanocapsules as a vehicle for controlled release of bioactive compounds. Carbohydr Polym 2015;115:1−9.
[57] Rivera MC, Pinheiro AC, Bourbon AI, Cerqueira MA, Vicente AA. Hollow chitosan/alginate nanocapsules for bioactive compound delivery. Int J Biol Macromol 2015;79:95−102.
[58] Aditya NP, Macedo AS, Doktorovova S, Souto EB, Kim S, Chang PS, Ko S. Development and evaluation of lipid nanocarriers for quercetin delivery: a comparative study of solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid nanoemulsions (LNE). LWT − Food Sci Technol (Lebensmittel−Wissenschaft -Technol) 2014;59: 115−21.
[59] Souza MP, Vaz AFM, Correia MTS, Cerqueira MA, Vicente AA, Carneiroda- Cunha MG. Quercetin-loaded lecithin/chitosan nanoparticles for functional food applications. Food Bioprocess Technol 2013;7: 1149−59.
[60] Sari TP, Mann B, Kumar R, B Singh RR, Sharma R, Bhardwaj M, Athira S. Preparation and characterization of nanoemulsion encapsulating curcumin. Food Hydrocolloids 2015;43:540−6.
[61] Silva HI, Cerqueira MC, Vicente AN. Nanoemulsions for food applications: development and characterization. Food Bioprocess Technol 2012;5: 854−67.
[62] Isailović BD, Kostić IT, Zvonar A, Đorđević VB, Gašperlin M, Nedović VA, Bugarski BM. Resveratrol loaded liposomes produced by different techniques, Innovative. Food Sci Emerg Technol 2013;19:181−9.
[63] Madhusudana Rao K, Krishna Rao KS, Ramanjaneyulu G, Ha CS. Curcumin encapsulated pH sensitive gelatin based interpenetrating polymeric network nanogels for anti cancer drug delivery. Int J Pharm 2015;478:788−95.
[64] Hu K, Huang X, Gao Y, Huang X, Xiao H, McClements DJ. Core-shell biopolymer nanoparticle delivery systems: synthesis and characterization of curcumin fortified zein-pectin nanoparticles. Food Chem 2015;182:275−81.

[65] Nallamuthu I, Devi A, Khanum F. Chlorogenic acid loaded chitosan nanoparticles with sustained release property, retained antioxidant activity and enhanced bioavailability. Asian J Pharm Sci 2015; 10:203–11.

[66] Hosseini SMH, Emam-Djomeh Z, Sabatino P, Van der Meeren P. Nanocomplexes arising from protein-polysaccharide electrostatic interaction as a promising carrier for nutraceutical compounds. Food Hydrocolloids 2015;50:16–26.

[67] Kakran M, Shegokar R, Sahoo NG, Gohla S, Li L, Müller RM. Long-term stability of quercetin nanocrystals prepared by different methods. J Pharm Pharmacol 2012;64:1394–402.

[68] Wei Q, Keck CM, Müller RH. Solidification of hesperidin nanosuspension by spray drying optimized by design of experiment (DoE). Drug Dev Ind Pharm 2018;44:1–12.

[69] Al Shaal L, Mishra PR, Müller RH, Keck C. Nanosuspensions of hesperetin: preparation and characterization. Die Pharmazie 2014;69:173–82.

[70] Mauludin R, Müller RH, Keck CM. Development of an oral rutin nanocrystal formulation. Int J Pharm 2009;370:202–9.

[71] Kobierski S, Ofori-Kwakye K, Müller RH, Keck CM. Resveratrol nanosuspensions: interaction of preservatives with nanocrystal production. Die Pharmazie 2011;66:942–7.

[72] Al Shaal L, Shegokar R, Müller RH. Production and characterization of antioxidant apigenin nanocrystals as a novel UV skin protective formulation. Int J Pharm 2011;420:133–40.

[73] Rachmawati H, Al Shaal L, Müller RH, Keck CM. Development of curcumin nanocrystal: physical aspects. J Pharm Sci 2013;102:204–14.

[74] Choi YH, Han HK. Nanomedicines: current status and future perspectives in aspect of drug delivery and pharmacokinetics. J Pharm Investig 2018;48: 43–60.

[75] Bonechi C, Martini S, Ciani L, Lamponi S, Rebmann H, Rossi C, Ristori S. Using liposomes as carriers for polyphenolic compounds: the case of trans-resveratrol. PLoS One 2012;7:e41438.

[76] Cavalcanti IMF, Menezes TGC, Campos LAA, Ferraz MS, V Maciel MA, P Caetano MN, Santos-Magalhães NS. Interaction study between vancomycin and liposomes containing natural compounds against methicillin-resistant *Staphylococcus aureus* clinical isolates. Braz J Pharm Sci 2018;54: e00203.

[77] Vijayakumar MR, Vajanthri KY, Balavigneswaran CK, Mahto SK, Mishra N, Muthu MS, et al. Pharmacokinetics, biodistribution, *in vitro* cytotoxicity and biocompatibility of Vitamin E TPGS coated trans resveratrol liposomes. Colloids Surf B Biointerfaces 2016d;145:479–91.

[78] Kumari S, Kumaraswamy RV, Choudhary RC, Sharma SS, Pal A, Raliya R, Biswas P, Saharan V. Thymol nanoemulsion exhibits potential antibacterial activity against bacterial pustule disease and growth promotory effect on soybean. Sci Rep 2018; 8:6650.

[79] Mitri K, Shegokar R, Gohla S, Anselmi C, Müller R. Lipid nanocarriers for dermal delivery of lutein: preparation, characterization, stability and performance. Int J Pharm 2011;414:267–75.

[80] Shofia SI, Jayakumar K, Mukherjee A, Chandrasekaran N. Efficiency of brown seaweed (*Sargassum longifolium*) polysaccharides encapsulated in nanoemulsion and nanostructured lipid carrier against colon cancer cell lines HCT 116. RSC Adv 2018;8:15973–84.

[81] Rachmawati H, Novel MA, Nisa RM, Berlian G, Tandrasasmita OM, Rahma A, Riani C, Tjandrawinata RR. Co-delivery of curcumin-loaded nanoemulsion and Phaleria macrocarpa extract to NIH 3T3 cell for antifibrosis. J Drug Deliv Sci Technol 2017;39:123–30.

[82] Rachmawati H, Meylina L, Rahma A, Sumirtapura YC. Size-dependent of oil droplet of curcumin nanoemulsion on the *in vivo* release kinetic of curcumin after oral and intravenous administrations in animal model. Adv Sci Eng Med 2014;6:959–64.

[83] Rachmawati H, Budiputra DK, Mauludin R. Curcumin nanoemulsion for transdermal application: formulation and evaluation. Drug Dev Ind Pharm 2015;41:560–6.

[84] Vijayanand P, Jyothi V, Aditya N, Mounika A. Development and characterization of solid lipid nanoparticles containing herbal extract: *in vivo* antidepressant activity. J Drug Deliv 2010;2018: 2908626.

[85] Donsi F, Sessa M, Ferrari G. Nanoencapsulation of essential oils to enhance their antimicrobial activity in foods. J Biotechnol 2010;150:67.

[86] Mulik RS, Mönkkönen J, Juvonen RO, Mahadik KR, Paradkar AR. Transferrin mediated solid lipid nanoparticles containing curcumin: enhanced *in vitro* anticancer activity by induction of apoptosis. Int J Pharm 2010;398:190–203.

[87] Jenning V, Gysler A, Schäfer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm 2000;49:211–8.

[88] Odei-Addo F, Shegokar R, Muller RH, Levendal RA, Frost C. Nanoformulation of *Leonotis leonurus* to

improve its bioavailability as a potential antidiabetic drug. Biotech 2017;7:344.

[89] Madureira AR, Nunes S, Campos DA, Fernandes JC, Marques C, Zuzarte M, Gullón B, Rodríguez-Alcalá LM, Calhau C, Sarmento B, Gomes AM, Pintado MM, Reis F. Safety profile of solid lipid nanoparticles loaded with rosmarinic acid for oral use: *in vitro* and animal approaches. Int J Nanomed 2016; 11:3621−40.

[90] Hu LD, Xing Q, Meng J, Shang C. Preparation and enhanced oral bioavailability of cryptotanshinone-loaded solid lipid nanoparticles. AAPS Pharm Sci Tech 2010;11:582−7.

[91] Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. Design and characterization of astaxanthin-loaded nanostructured lipid carriers. Innov Food Sci Emerg Technol 2014;26:366−74.

[92] Manea AM, Vasile BS, Meghea A. Antioxidant and antimicrobial activities of green tea extract loaded into nanostructured lipid carriers. Compt Rendus Chem 2014;17:331−41.

[93] Okonogi S, Riangjanapatee P. Physicochemical characterization of lycopene-loaded nanostructured lipid carrier formulations for topical administration. Int J Pharm 2015;478:726−35.

[94] Rachmawati H, Novel MA, Ayu S, Berlian G, Tandrasasmita OM, Tjandrawinata RR, Anggadiredja K. The *in vitro-in vivo* safety confirmation of PEG-40 hydrogenated castor oil as a surfactant for oral nanoemulsion formulation. Sci Pharm 2017; 85:18−27.

[95] Yi J, Lam TI, Yokoyama W, Cheng LW, Zhong F. Cellular uptake of β-carotene from protein stabilized solid lipid nanoparticles prepared by homogenization−evaporation method. J Agric Food Chem 2014;62:1096−104.

[96] Ma J, Guan R, Shen H, Lu F, Xiao C, Liu M, Kang T. Comparison of anticancer activity between lactoferrin nanoliposome and lactoferrin in Caco-2 cells *in vitro*. Food Chem Toxicol 2013;59:72−7.

[97] Sessa M, Balestrieri ML, Ferrari G, Servillo L, Castaldo D, D'Onofrio N, Donsì F, Tsao R. Bioavailability of encapsulated resveratrol into nanoemulsion-based delivery systems. Food Chem 2014;147:42−50.

[98] Li M, Cui J, Ngadi MO, Ma Y. Absorption mechanism of whey-protein delivered curcumin using Caco-2 cell monolayers. Food Chem 2015;180:48−54.

[99] Araújo F, Shrestha N, Shahbazi MA, Fonte P, Mäkilä EM, Salonen JJ, Hirvonen JT, Granja PL, Santos HA, Sarmento B. The impact of nanoparticles on the mucosal translocation and transport of GLP-1 across the intestinal epithelium. Biomaterials 2014; 35:9199−207.

[100] Hu B, Xie M, Zhang C, Zeng X. Genipin-structured peptide−polysaccharide nanoparticles with significantly improved resistance to harsh gastrointestinal environments and their potential for oral delivery of polyphenols. J Agric Food Chem 2014;62:12443−52.

[101] P Dandekar P, Jain R, Patil S, Dhumal R, Tiwari D, Sharma S, Vanage G, Patravale V. Curcumin-loaded hydrogel nanoparticles: application in antimalarial therapy and toxicological evaluation. J Pharm Sci 2010;99:4992−5010.

[102] Forth W, Henschler D, Rummel W. Pharmacology and toxicology. For students of medicine, veterinary medicine, pharmacy, chemistry, biology as well as for physicians, veterinarians and pharmacists. Food and Agriculture Organization of the United Nations; 1987.

[103] Innes NP, Ogden GR. A Technique for the study of endocytosis in human oral epithelial cells. Arch Oral Biol 1999;44:519−23.

[104] Jung T, Kamm W, Breitenbach A, Kaiserling E, Xiao JX, Kissel T. Biodegradable nanoparticles for oral delivery of peptides: is there a role for polymers to affect mucosal uptake. Eur J Pharm Biopharm 2000;50:147−60.

[105] Frohlich E, Roblegg E. Models for oral uptake of nanoparticles in consumer products. Toxicology 2012;291: 10−7.

[106] Asati A, Santra S, Kaittanis C, Perez JM. Surface-charge-dependent cell localization and cytotoxicity of cerium oxide nanoparticles. ACS Nano 2010;4: 5321−31.

[107] Cho EC, Au L, Zhang Q, Xia Y. The effects of size, shape, and surface functional group of gold nanostructures on their adsorption and internalization by cells. Small 2010;6:517−22.

[108] Holpuch AS, Hummel GJ, Tong M, Seghi GA, Pei P, Ma P, Mumper RJ, Mallery SR. Nanoparticles for local drug delivery to the oral mucosa: proof of principle studies. Pharm Res 2010;27:1224−36.

[109] Elder A, Vidyasagar S, DeLouise L. Physicochemical factors that affect metal and metal oxide nanoparticle passage across epithelial barriers. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2009;1:434−50.

[110] Van der Lubben IM, Verhoef JC, Borchard G, Junginger HE. Chitosan and its derivatives in mucosal drug and vaccine delivery. Eur J Pharm Sci 2001;14: 201−7.

[111] Card JW, Zeldin DC, Bonner JC JC, Nestmann ER. Pulmonary applications and toxicity of engineered

nanoparticles. Am J Physiol Lung Cell Mol Physiol 2008;295:L400–11.
[112] Sarin H, Kanevsky AS, Wu H, Brimacombe KR, Fung SH, Sousa AA, Auh S, Wilson CM, Sharma K, Aronova MA, Leapman RD, Griffiths GL, Hall MD. Effective transvascular delivery of nanoparticles across the blood-brain tumor barrier into malignant glioma cells. J Transl Med 2008;6:1–15.
[113] Lu W, Kelly AL, Maguire P, Zhang H, Stanton C, Miao S. Correlation of emulsion structure with cellular uptake behavior of encapsulated bioactive nutrients: influence of droplet size and interfacial structure. J Agric Food Chem 2016;64:8659–66.
[114] Tan TB, Chu WC, Yussof NS, Abas F, Mirhosseini H, Cheah YK, Nehdi IA, Tan CP. Physicochemical, morphological and cellular uptake properties of lutein nanodispersions prepared by using surfactants with different stabilizing mechanisms. Food Funct 2016;7: 2043–51.
[115] Ganesan P, Ramalingam P, Karthivashan G, Ko YT, Choi DK. Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phytobioactive compounds in various chronic diseases. Int J Nanomed 2018;13:1569–83.
[116] Baek JS, Cho CW. Surface modification of solid lipid nanoparticles for oral delivery of curcumin: improvement of bioavailability through enhanced cellular uptake, and lymphatic uptake. Eur J Pharm Biopharm 2017;117:132–40.
[117] Ramalingam P, Ko YT. Validated LC-MS/MS method for simultaneous quantification of resveratrol levels in mouse plasma and brain and its application to pharmacokinetic and brain distribution studies. J Pharm Biomed Anal 2016;119:71–5.
[118] Fathi M, Mirlohi M, Varshosaz J, Madani G. Novel caffeic acid nanocarrier: production, characterization, and release modeling. J Nanomater 2013:434632.
[119] Ramalingam P, Ko YT. Enhanced oral delivery of curcumin from N-trimethyl chitosan surface-modified solid lipid nanoparticles: pharmacokinetic and brain distribution evaluations. Pharm Res 2015;32:389–402.
[120] Ramalingam P, Ko YT. Improved oral delivery of resveratrol from N-trimethyl chitosan-g-palmitic acid surface-modified solid lipid nanoparticles. Colloids Surf B Biointerfaces 2016;139:52–61.
[121] Yang S. Preparation, *in vitro* characterization and pharmacokinetic study of coenzyme Q10 long-circulating liposomes. Drug Res (Stuttg) 2018;68: 270–9.
[122] Liang R, Shoemaker CF, Yang X, Zhong F, Huang Q. Stability and bioaccessibility of β-carotene in nanoemulsions stabilized by modified starches. J Agric Food Chem 2013;61:1249–57.
[123] Ha TVA, Kim S, Choi Y, Kwak HS, Lee SJ, Wen J, Oey I, Ko S. Antioxidant activity and bioaccessibility of size-different nanoemulsions for lycopene-enriched tomato extract. Food Chem 2015;178: 115–21.
[124] Qian C, Decker EA, Xiao H, McClements DJ. Nanoemulsion delivery systems: influence of carrier oil on β-carotene bioaccessibility. Food Chem 2012;135: 1440–7.
[125] Davidov-Pardo G, Pérez-Ciordia S, R Marín-Arroyo MA, McClements DJ. Improving resveratrol bioaccessibility using biopolymer nanoparticles and complexes: impact of protein–carbohydrate Maillard conjugation. J Agric Food Chem 2015;63: 3915–23.
[126] Nallamuthu I, Khanum F, Fathima SJ, Patil MM, Anand T. Enhanced nutrient delivery through nanoencapsulation techniques: the current trend in food industry. In: Book: nutrient delivery. Elsevier; September 2016. p. 619.
[127] Penalva R, Esparza I, Agüeros M, Gonzalez-Navarro CJ, Gonzalez-Ferrero C, M Irache J. Casein nanoparticles as carriers for the oral delivery of folic acid. Food Hydrocolloids 2015;44:399–406.
[128] Hatanaka J, Chikamori H, Sato H, Uchida S, Debari K, Onoue S, Yamada S. Physicochemical and pharmacological characterization of α-tocopherol-loaded nanoemulsion system. Int J Pharm 2010;396:188–93.
[129] Faisal W, Ruane-O'Hora T, O'Driscoll CM, Griffin BT. A novel lipid-based solid dispersion for enhancing oral bioavailability of Lycopene: *in vivo* evaluation using a pig model. Int J Pharm 2013;453:307–14.
[130] Kamil A, Smith DE, Blumberg JB, Astete C, Sabliov C, O Chen CY. Bioavailability and biodistribution of nanodelivered lutein. Food Chem 2016;192:915–23.
[131] Arunkumar R, Prashanth KVH, Baskaran V. Promising interaction between nanoencapsulated lutein with low molecular weight chitosan: characterization and bioavailability of lutein *in vitro* and *in vivo*. Food Chem 2013;141:327–37.
[132] Shangguan M, Qi J, Lu Y, Wu W. Comparison of the oral bioavailability of silymarin-loaded lipid nanoparticles with their artificial lipolysate counterparts: implications on the contribution of integral structure. Int J Pharm 2015;489:195–202.
[133] Shelma R, Sharma CP. *In vitro* and *in vivo* evaluation of curcumin loaded lauroyl sulphated chitosan for enhancing oral bioavailability. Carbohydr Polym 2013;95:441–8.

[134] Chaurasia S, Patel RR, Chaubey P, Kumar N, Khan G, Mishra B. Lipopolysaccharide based oral nanocarriers for the improvement of bioavailability and anticancer efficacy of curcumin. Carbohydr Polym 2015;130: 9–17.

[135] Okawara M, Hashimoto F, Todo H, Sugibayashi K, Tokudome Y. Effect of liquid crystals with cyclodextrin on the bioavailability of a poorly water-soluble compound, diosgenin, after its oral administration to rats. Int J Pharm 2014;472:257–61.

[136] Zhang J, Huang Y, Liu D, Gao Y, Qian S. Preparation of apigenin nanocrystals using supercritical antisolvent process for dissolution and bioavailability enhancement. Eur J Pharm Sci 2013;48:740–7.

[137] Zhu Y, Peng W, Zhang J, Wang M, Firempong CK, Feng C, Yu J. Enhanced oral bioavailability of capsaicin in mixed polymeric micelles: preparation, *in vitro* and *in vivo* evaluation. J Funct Foods 2014;8: 358–66.

[138] Pandita D, Kumar S, Poonia N, Lather V. Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Res Int 2014;62: 1165–74.

[139] Liang W, Lou M, Si W. Nano anticancer micelles of vinca alkaloids entrapped in polyethylene glycolated phospholipids. US Patent 20090053293 A1 J Nano Res February 26, 2009;3439:12.

[140] Zale SE, Troiana G, Ali MM, Hrkach J, Wright J. Therapeutic polymeric nanoparticles comprising vinca alkaloids and methods of making and using them. April 29, 2010. US Patent 20100104655 A1.

[141] Rigas B, Mackenzie G, Yu S, Huang L, Zhu R, Nie T. Combination treatments and formulations for cancer. October 20, 2011. WO Patent 2011130486 A2.

[142] Einbond L, Redenti S. Growth inhibitoyr effects of nanoparticles containing triterpene glycosides or triterpenes. July 11, 2013. US Patent 2013/0177657 A1.