HERBAL SUPPLEMENTS and the BRAIN
Understanding their Health Benefits and Hazards

S.J. Enna  Stata Norton
Praise for Herbal Supplements and the Brain

“Both skeptics and believers in the value of herbal supplements for brain conditions will enjoy the calm objective analysis to which these two experienced pharmacologists put the most popular products. You may not like their conclusions, but their evidence is convincing.”

—Floyd E. Bloom, MD, Professor Emeritus, Molecular and Integrative Neuroscience Department, TSRI

“Written with authority yet as lucid and enticing as a novel, the Enna/Norton book is certainly the finest volume I know addressing the interface of herbs, the brain, and behavior. It will be of value and fun for the educated layperson as well as the professional.”

—Solomon H. Snyder, M.D., Department of Neuroscience, Johns Hopkins University School of Medicine

“It all began with Adam’s apple. Knowing what you add to your diet may change your life. Getting a kick from a cup of coffee, fighting depression with St. John’s wort, drifting away with valerian, or reaching a ripe old age with Gingko, this book gives insights into the pros and cons of taking herbal supplements. Excellent and entertaining reading!”

—Hanns Möhler, Professor of Pharmacology, University of Zurich, Switzerland

“If you are someone who takes and believes in herbal supplements, then this book is a must-read for you. I’ll bet you will be surprised at some of the information. It is written by two extraordinarily qualified authors, who have decades of experience with the effects and toxicities of drugs and supplements. The aim of the book is to use proven criteria to evaluate if herbal supplements are effective or not. This information is not always easy to find, so read on.”

—Michael J Kuhar, Ph.D., Yerkes National Primate Research Center of Emory University, Candler Professor of Neuropharmacology, School of Medicine, Georgia Research Alliance Eminent Scholar, Center for Ethics of Emory University
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Illustrated by Kevin S. Smith
We thank our spouses, Colleen Enna and David Ringle, for the decades they have devoted to encouraging us to pursue our scientific interests and career goals. Neither this book, nor any of our other accomplishments, would have been possible without their patience, support, and understanding. This work is dedicated to them.
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## Contents

Preface ........................................... xvi

Chapter 1  The Gifts of Eden ....................... 1

Chapter 2  Transforming Plants into Gold ......... 7
  Prehistoric Evidence .......................... 8
  Early Documentation ......................... 9
  Western Culture ............................. 11
  Alchemy .................................... 13
  Chemistry .................................. 15

Chapter 3  Thinking Like a Pharmacologist...... 17
  The Origins of Pharmacology ................. 19
  Pharmacodynamics .......................... 21
  Pharmacokinetics ........................... 24
  In Vitro and In Vivo Studies .................. 27
  Pharmacology and Herbal Supplements ..... 27
  Herbal Supplement Pharmacology Checklist .. 28

Chapter 4  The Brain as a Drug Target .......... 33
  The Human Brain ............................ 36
  Chemical Neurotransmission ................. 39
  Neurotransmitter Systems .................... 41
  Behavioral Assays ........................... 45
  Clinical Studies ............................ 49

Chapter 5  Ginkgo (Ginkgo biloba) ................. 53
  Botany .................................... 55
  Therapeutic Uses ............................ 55
  Constituents ................................. 57
  Pharmacokinetics ........................... 59
  Pharmacodynamics .......................... 61
  Adverse Effects ............................. 65
  Pharmacological Perspective ............... 66
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Preface

While for more than 200,000 years humans have been consuming plant materials, such as flowers, fruits, leaves, and roots, for therapeutic benefit, it is only in the last 150 years that scientists have been able to isolate, identify, examine, and categorize the biologically active constituents in plants. Many of the compounds identified, or chemical derivatives of them, are now employed as drugs. The ability to obtain such precise scientific information, and to synthesize other active compounds, opened the way for legislators in the early twentieth century to enact laws regulating the marketing and sale of chemicals for therapeutic purposes. The creation of these regulatory requirements was spurred by the fact that many inert, and sometimes toxic, products were sold as medications to the public. Current laws mandate that any substance marketed as a treatment for a particular condition must first undergo rigorous testing in laboratory animals and humans to demonstrate its safety and effectiveness.

Although prescription and over-the-counter medications are subject to tight federal oversight, there are few regulations concerning the sale of herbal supplements. In the United States, the chief requirement is that no formal claims be made of any therapeutic benefit resulting from the use of these products. Nonetheless, consumers are continuously exposed in the lay press and online to reports on the purported curative properties of certain herbs or how their consumption can help prevent disease. Such reports are no doubt responsible for driving sales in this multibillion dollar industry. However, like our ancient ancestors, today’s consumer may be purchasing and consuming these products for health benefits based solely on the word of others, not as a result of an independent and objective analysis of the data supporting the claims. This is understandable, as most lack the technical background for making an informed scientific judgment. The aim of this book is to address this need.

Herbal products are used around the world for a variety of purposes. Among these is the treatment of central nervous system disorders, such as anxiety, insomnia, alcoholism, dementia, and depression. Herbal supplements are also taken to modify brain function in the
treatment of other conditions, such as chronic pain and obesity. Because some of the symptoms of these disorders resolve over time without medication, and many have a strong psychological component, it is often difficult to prove the efficacy of an herbal product as a treatment for these conditions. That is, while the effectiveness of a dietary supplement that reduces body weight would be apparent, the contribution of an herbal product in lessening feelings of depression, or in enhancing cognitive abilities, is more difficult to quantify. For this reason, the claims for such benefits may not be supported by experimental data. In this regard, the consumer may be no different than the primitive who ingested a plant material to alter his mental status. Sometimes it worked; often it did not. A change in perception or feelings, or in sleep patterns, could be the result of an active constituent in the plant, or the power of suggestion. Prolonged consumption of any product with no inherent value is not only costly, but potentially dangerous as anything taken into the body can have toxic consequences. This volume is devoted to a discussion of herbal supplements taken to affect brain function because of the unique challenges associated with assessing the effectiveness of such products.

Written for the nonscientist, the book is informally divided into two parts. The first section, chapters 1–4, provides an historical perspective on the use of plant products to modify central nervous system function and on the development of the techniques employed for drug discovery. Included is a discussion of the basic principles of pharmacology, the science of drugs, as they relate to assessing the potential effectiveness and safety of an herbal supplement. Descriptions are provided of the components of the central nervous system that are dysfunctional in neurological and psychiatric disorders, and the targets of drugs used to treat these conditions. Taking all of these issues into consideration, a short checklist is provided to assist the potential consumer in determining, from a scientific standpoint, whether a particular product is likely to contain chemicals that beneficially affect brain function. The reader is encouraged to complete the first four chapters before proceeding to those describing individual plant products. The introductory chapters provide the context, concepts, and definitions essential for understanding fully the reasoning and conclusions drawn in the second part of the book.
Chapters 5 through 15 are devoted to a scientific assessment of the claims made for a select group of herbal products that are believed to have central nervous system effects. The pharmacological principles provided in the earlier chapters are applied in this analysis, with the checklist items used to guide the reader in the search for the truth. In this way, the reader can appreciate how answering a few key questions yields powerful insights into the potential benefit of these products.

The primary audience for this book is consumers interested in determining the value of herbal products purported to influence brain function. Others who will find this information of interest and value are students considering careers in the neurosciences or drug discovery, and scientists seeking an updated review of this field. By having the tools needed to make an objective and scientific assessment of these products, consumers are in a much better position to maximize the benefits of herbal supplements. This information will also make it possible to minimize the risks to one's health that comes with consuming these substances without adequate information on their effectiveness and safety.
Adam wasn’t hungry and was apprehensive about the potential consequences of eating the forbidden fruit. He was, however, convinced the plant material could provide benefits beyond its nutritional value. On the one hand, God told him that its consumption would be fatal, while the serpent contended the plant would impart new knowledge. Both were right. After eating the fruit Adam lost his home and immortality, and was made aware of the concepts of good and evil. He would need this new knowledge to survive in the world outside of Eden.

Besides its allegorical importance for Jews, Christians, and Muslims, this biblical account provides lessons for those interested in the therapeutic benefits of herbal supplements, also known as nutritional, dietary, or food supplements. Defined as a product that contains a vitamin, mineral, herb or other botanical, an amino acid, an extract, or any combination of these materials, the United States government considers dietary supplements to be foods rather than drugs. This has
significant implications with regard to their regulation and the assurances provided to consumers. Because of this categorization, potential users must obtain on their own objective data about these products. The aim of this book is to provide such information.

The most fundamental question pertaining to dietary supplements is whether there is any evidence that they provide benefits beyond possible nutritional value. Written some 2,500 years ago, the Genesis account of Adam’s introduction to these products indicates that humans have been familiar with the possible mystical and therapeutic powers of plants for quite some time. Moreover, the Old Testament account demonstrates that then, as now, there was uncertainty, and therefore risk, associated with the consumption of plants and plant products for religious, therapeutic, or, as in Adam’s case, educational purposes.

The fruit consumed by Adam is unknown. In Old English, the word “apple” is simply a synonym for fruit. Regardless, when tempted to eat the plant product, Adam was at a distinct disadvantage to today’s consumer. There was no historical record on its possible effects and no scientific data on its safety. Moreover, as the basic principles of pharmacology, the science of drugs, had not yet been established, he was unable to assess these properties himself. Rather, Adam had to rely solely on the word of others.

The constraints experienced by Adam remained for thousands of years until written records were maintained on the medicinal value of plants. More centuries passed before chemists were able to identify, and pharmacologists objectively study, the therapeutically active constituents in plant and animal products. Only during the past century has research revealed the diseases and disorders that are most responsive to these constituents, and to define precisely the appropriate doses to maximize safety and effectiveness in most individuals.

Anecdotal accounts about the potential benefits of dietary supplements have existed for thousands of years. Evidence includes pollen grains found on Neanderthal (Homo neanderthalensis) graves that were from plants lacking showy flowers, such as the yarrow (Achillea millefolium). It is inferred that these plants were placed there not for adornment, but to provide the departed a supply of medications in the afterlife. This concept is based, in part, on the fact that many of the plants deposited on Neanderthal gravesites were
subsequently described as therapeutics in early medical books, indicating that word of their therapeutic powers was passed on for millennia. For example, yarrow is mentioned in the Assyrian Herbal (800 BC), one of the oldest listings of therapeutically active plant products, as well as in the Ebers papyrus (1500 BC) from Egypt. The Greek poet Homer described in *The Iliad* (800 BC) the use of yarrow to cure wounds, as did the Roman naturalist Pliny the Elder in his writings during the first century AD.

A conservative estimate is that plants have been used as therapeutics at least since the appearance of modern man, some 200,000 years ago. It seems reasonable that as early humans foraged for food they would accidently discover the curative powers of some plants or take note of the fact that consumption of a certain type of seed, root, or fruit produced discernable effects on mood, sensory input, or alleviated general aches and pains. Indeed, as a species, humans are indebted to the many thousands of forgotten ancestors who became ill or died in the process of identifying plants and animals suitable for consumption. Thus, through trial and error, early man was able to identify plants that possess useful medicinal properties.

In addition to using plants to cure disease, they were also consumed in the ongoing quest for immortality. Recipes for “elixirs of life” were described in ancient writings. An example is the *Epic of Gilgamesh*, the story of a Sumarian hero that was recorded in 2000 BC. After many travails, Gilgamesh obtained the plant of immortality from deep in the sea. Unfortunately for Gilgamesh, the plant was subsequently stolen by a serpent. This tale has many of the features of the biblical account of Adam and Eve. In the end, Gilgamesh returned home to Sumer to, like the rest of us, spend the remainder of his days as a mortal, awaiting the inevitable.

As in Genesis, ancient medical texts demonstrate that plant products have been used for therapeutic purposes for millennia. During most of this time no concerted effort was made to understand the reason for their effectiveness, or, in modern terminology, their mechanism of action. The first recorded attempts to synthesize therapeutics were made by European alchemists during the Middle Ages. Besides their efforts to transform base metals into gold, the alchemists were interested in what made substances therapeutically
useful as they wanted the power to transform basic materials into drugs. They were hindered in this quest, however, by the prevailing theories about the nature of matter and the causes of disease.

From the time of Aristotle to the seventeenth century, the use of plants in European medicine was based on the idea that all nature was composed of four basic elements: earth, air, fire, and water. Disease resulted from an imbalance of bodily humors. It was believed this imbalance could be countered by one or more of the four plant classes—cold, dry, hot, and wet—that corresponded to the four basic elements of nature. Mixtures of plants, usually from the same class, were preferred over a single specimen for treating medical conditions. For example, combinations of “cold” plants were used to treat fevers. Given these theories, drug discovery remained an empirical enterprise for thousands of years, with the identification of active plants and plant products left solely to chance.

By the seventeenth century, belief in the Aristotelian four elements was being challenged, most notably by the Irish chemist Robert Boyle. Boyle understood that the precise identification and classification of the basic elements of nature were absolutely essential for understanding the universe, including drug actions. Thanks to his efforts, and those of many others, modern chemistry emerged in the nineteenth century. This made it possible to isolate, chemically define, and study the biological responses to plant constituents. As a result of these efforts, drugs were identified in plants that were first discovered by our distant ancestors. Many of these compounds, or their chemical derivatives, are still used today.

Given the historical records, and contemporary scientific data, there is no question that plants produce an abundance of substances that provide benefits beyond their nutritional value. However, not all plant constituents have been isolated and properly tested for effectiveness, and, unlike drugs, there is no government requirement that a manufacturer demonstrate effectiveness before marketing an herbal supplement. Like Adam, the consumer must rely on the word of others about the benefits of these products.

This book is designed to address this issue by providing basic information needed to assess the potential therapeutic value of plant products. Included are fundamental principles of pharmacology and
about how drugs and natural products can affect various organs and organ systems. Explanations and examples are provided about what determines whether an ingested substance will find its way into the bloodstream, and then to the targeted site in the body at a concentration sufficient to have a beneficial effect. Other topics include the ways in which natural products may influence the blood levels of other substances, including drugs, and the likelihood that such interactions may diminish the effectiveness of prescription medications or alter normal body chemistry. While the principles described apply to all dietary supplements and drugs, emphasis is placed on factors that relate especially to herbal supplements purported to influence brain function. Individual chapters are devoted to a discussion of selected nutritional supplements that are said to enhance memory, or to aid in the treatment of depression, anxiety, insomnia, and alcoholism. These products were chosen because the promised benefits can be difficult to quantify and are more subject to influence by the power of persuasion than is the case with other therapeutics. This is why the use of such substances has been exploited over the centuries by shamans to maintain their social standing, and by charlatans for monetary gain. The properties of these products are described in the context of the basic principles of pharmacology and the results of scientific studies, both human and laboratory animal, aimed at determining effectiveness and mechanism of action. The approach taken in objectively evaluating these products can be used by the reader as a guide for assessing the information available on any dietary supplement. This work is intended for those who are curious about the potential benefits and risks associated with the use of food supplements. The information provided will be of particular value for individuals who, like Adam, are interested in how drugs and natural products affect us for good and evil.
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acetaldehyde, 145
acetoxyvalerenic acid, 89
acetylcholine, 22, 42-44
acetylcholine neurotransmission, effects of lavender (Lavandula angustiolia) on, 133
acetylcholine nicotinic receptor system, 155
acetylcholinesterase, 103, 133-134, 155-156
acetylsalicylic acid (aspirin), 21
Achillea millefolium (yarrow) presence in Neanderthal graves, 2, 8
use in Greco-Roman era, 3
adenosine, 42-43, 185
Adlumia fungosa, 43
adverse effects of cocoa (Theobroma cacao), 186-187
of coffee (Coffea arabica), 186-187
of daffodil (Narcissus pseudonarcissus), 158-159
of ginkgo (Ginkgo biloba), 65-66
of kava (Piper methysticum), 118-120
of kudzu (Pueraria lobata), 146-147
of lavender (Lavandula angustiolia), 134-135
of lemon balm (Melissa officinalis), 106
of passion flower (Passiflora incarnata), 173
of St. John’s wort (Hypericum perforatum), 80-81
of tea (Camellia sinensis), 186-187
of Valeriana officinalis (Valerian), 93-94
aglycones, 140-142
agonists, 23
alchemy, 3-4, 13-15
alcohol withdrawal, therapeutic use of kudzu (Pueraria lobata) for, 143-146
alcoholism, therapeutic use of kudzu (Pueraria lobata) for, 143-146
aldehyde dehydrogenase-2, 144-145
alkaloids, 192-193
caffeine
  adverse effects, 186-187
  chemical structure of, 181
  historical use of, 175-177
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 178-180
definition of, 149
in daffodil. See daffodil (Narcissus pseudonarcissus)
in passion flower (Passiflora incarnata), 164
theobromine, 180-181
  adverse effects, 186-187
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 179
theophylline, 180-181
  adverse effects, 186-187
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 179
alpha-pinene, 73
alprazolam, interaction with St. John’s wort, 80
Althea, presence in Neanderthal graves, 8
Alzheimer’s disease, 37, 47
Neuropsychiatric Inventory and Alzheimer’s Disease Assessment Scale, 50
therapeutic use of ginkgo (Ginkgo biloba), 64
therapeutic use of lemon balm (Melissa officinalis), 103
therapeutic use of lavender (Lavandula angustioliia), 130-132
therapeutic use of galantamine, 155-157
Amaryllidaceae, 151-153
amitriptyline, interaction with St. John’s wort, 80
amphetamine, 46, 191
amygdala, 37
analgesia, therapeutic use of lavender (Lavandula angustioliia) for, 130-131
analgesic effect
  of daffodil (Narcissus pseudonarcissus), 156
  of passion flower (Passiflora incarnata), 171
Andrea (Jesuatti Friar), 21
Andrea, Giovanni, 14
anecdotal reports, 49
Anethum graveolens (dill seed), 12
animal test models, 46-48
antagonists, 23
anthrones, 72
anti-inflammatory effect
  of daffodil (Narcissus pseudonarcissus), 157
  of passion flower (Passiflora incarnata), 172
anticonvulsant effect
of lavender (Lavandula angustiolia), 130
of passion flower extract, 170
antimicrobial properties of lavender (Lavandula angustiolia), 131
antioxidant activity of lemon balm (Melissa officinalis), 104
antitumor activity of daffodil (Narcissus pseudonarcissus), 157
anxiety
therapeutic use of kava (Piper methysticum), 116-117
therapeutic use of lemon balm (Melissa officinalis), 102-105
therapeutic use of lavender (Lavandula angustiolia), 129-134
therapeutic use of passion flower (Passiflora incarnata), 168-170
therapeutic use of Valerian (Valeriana officinalis), 90-93
apigenin, 164-169
apolinaris (Hyoscyamus), 13
apoptosis, effect of ginkgo (Ginkgo biloba) on, 62
Aristotle, 12
aromatase, 172
Ascyrum (St. Peter’s wort), 70
aspirin (acetylsalicylic acid), 21
assays, behavioral, 45-48
Assyrian Herbal, 3, 10-11
Atropa belladonna, 23
awaine, 118
axo-axonic synapses, 40
axo-dendritic synapses, 40
axons, 36

B

Bacon, Francis, 15
barbiturates, 43, 83
behavioral assays, 45-48
Ben Cao Pin Hui Jing Yao (Liu Wen-Tai), 54-55
benzodiazepines, 43, 83
beta-amyloid, 47, 103
beta-caryophyllene, 73
beta-myrcene, 73
bianthaquinone, 72
Biblical mention of herbal supplements, 1
bicuculline, 43
bilobalide, 58-60
bioavailability, 24-26, 59-60
bornyl acetate, 87-88
botany
of cocoa (Theobroma cacao), 177-178
of coffee (Coffea arabica), 177-178
of daffodil (Narcissus pseudonarcissus), 151-152
of ginkgo (Ginkgo biloba), 55
of kava (Piper methysticum), 110-111
of kudzu (Pueraria lobata), 138-139
of lavender (Lavandula angustiolia), 124-125
of lemon balm (Melissa officinalis), 98
of passion flower (Passiflora incarnata), 162-163
of St. John’s wort (Hypericum perforatum), 69-70
of tea (Camellia sinensis), 177-178
of Valerian (Valeriana officinalis), 84-85
Boyle, Robert, 4, 15
brain
  chemical neurotransmission, 39-41
  neurotransmitter systems, 41-45
  nucleus accumbens, 114
  sigma receptors, 77
  structure of, 36-39

Caffeic acid, 182
Caffeine
  adverse effects, 186-187
  chemical structure of, 181
  historical use of, 175-177
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 178-180
Camellia japonica, 177-179
Camellia sinensis (tea), 11
  adverse effects, 186-187
  botany, 177-178
  constituents, 180-182
  historical use of, 175-177
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 178-180
Camphor, 126
Cannabinoids, 191
Cannabis, 191
  Cannabis sativa, 11, 191
  catechins, 182-185
  categorization of herbal supplements, 1, 18
  Catha edulis, 190
  caudate nucleus, 38
  Celsus, 12
  Centaurea (century plant), 8
  central nervous system, 33-35.
    See also brain
    central nervous system
    depressants, 83
    central nervous system disorders, 34
  century plant (Centaurea), 8
  cerebellum, 37-38
  cerebral cortex, 37-38
  challenges of pharmacological analysis of herbal supplements, 27-28
  chemical neurotransmission, 39-41
  chemistry, development of, 4, 15-16
  chloridiazepoxide (Librium®), 83
  chlorogenic acid, 182
  chocolate. See cocoa
  chrysin, 164-169, 172
  cingulate cortex, 37
  Cistus laudanifer, 20
  citral, 99-104
  citronellal, 99-104
  Clark, A. J., 24
  clinical depression, 67
  clinical studies, 49-51
  clovamide, 182
  Clusiaceae, 69
  cocaine, 191
  cocoa (Theobroma cacao)
    adverse effects, 186-187
    botany, 177-178
    constituents, 180-182
    historical use of, 175-177
    pharmacodynamics, 184-186
    pharmacokinetics, 182-184
pharmacological perspective, 187-188
therapeutic uses, 178-180
codeine, 190
Coffea arabica (coffee)
adverse effects, 186-187
botany, 177-178
constituents, 180-182
historical use of, 175-177
pharmacodynamics, 184-186
pharmacokinetics, 182-184
pharmacological perspective, 187-188
therapeutic uses, 178-180
Coffea canephora, 175
coffee (Coffea arabica)
adverse effects, 186-187
botany, 177-178
constituents, 180-182
historical use of, 175-177
pharmacodynamics, 184-186
pharmacokinetics, 182-184
pharmacological perspective, 187-188
therapeutic uses, 178-180
Commiphora myrrha, 9
Cook, James, 109
Corey, Elias James, 57
corpus striatum, 38
Crataeus, 12
crossover studies, 49
Culpepper, Nicholas, 124
cyclosporine, interaction with St. John’s wort, 80
cytochrome P450 enzymes, 26

D

daffodil (Narcissus pseudonarcissus), 149-151
adverse effects, 158-159
botany, 151-152
constituents, 153-154
historical use of, 152
pharmacodynamics, 155-158
pharmacokinetics, 154-155
pharmacological perspective, 159
therapeutic uses, 152
daidzein, 140-142, 146
daizin, 140, 144
Darwin, Charles, 109
De Medicina (Celsius), 12
dehyrogenase, 145
delta-9-tetrahydrocannabinol, 191
dementia. See Alzheimer’s disease
dendrites, 36
depression, therapeutic use of St. John’s wort for, 67-71, 75-80
desmethoxyangonin, 112-114, 120
dextromethorphan, interaction with St. John’s wort, 80
Dian Nan Ben Cao (Lan Mao), 54
diazepam (Valium®), 43, 83, 89
Dicentra cucullaria (Dutchman’s britches), 43
Dietary Supplement Health and Education Act of 1994, 18
diffusion, 25
Digenea simplex, 43
digoxin
interaction with lemon balm (Melissa officinalis), 101
interaction with St. John’s wort (Hypericum perforatum), 80
dihydrokavain, 112-114
dihydromethysticin, 112-114, 120
dill seed (Anethum graveolens), 12
donepezil, 156
dopamine, 36, 42-44
double-blind studies, 49
Dr. Willmar Schwabe GmbH & Company, 57, 132
drug receptors, discovery of, 22-24
Dutchman’s britches (Dicentra cucullaria), 43

E
early documentation of herbal supplements, 3, 9-11
Ebers papyrus, 3, 9
Ebers, George, 9
EGb 761, 57
Ehrlich, Paul, 22
elements, periodic table of, 16
elevated plus maze, 46
emetic effect of
daffodil (Narcissus pseudonarcissus), 157
endocannabinoids, 191
endogenous depression, 67
English lavender. See lavender (Lavandula angustiolia)
Enquiry into Plants (Theophrastus), 151
enterovirus 71, 157
enzymes
  acetylcholinesterase, 133, 155-156
  aldehyde dehydrogenase-2, 144-145
  aromatase, 172
  cytochrome P450 enzymes, 26
  5-lipoxygenase, 77
  nitric oxide synthase, 77
  phosphodiesterase, 184
Ephedra, 11
  Ephedra equisetina, 190
  Ephedra sinica, 190
  presence in Neanderthal graves, 8
ephrine, 8, 190-191
Epic of Gilgamesh, 3
epigalocatechin-3-gallate, 182, 185-187
Erythroxylon coca, 191
ethanol, 83
ethyl alcohol, 83
excitatory neurotransmitters, 40
extrapyramidal system, 38

F
FDA (Food and Drug Administration)
  establishment of, 17
  lack of oversight over herbal supplements, 18-19
  role of, 17-18
Federal Food, Drug, and Cosmetic Act, 17
fennel (Foeniculum vulgare), 12
5-lipoxygenase, 77
flavokawain B, 118-119
flavonoids
  bioavailability of, 59-60
  in cocoa (Theobroma cacao), 182
  in coffee (Coffea arabica), 182
  in ginkgo standardized extract, 58
  in kudzu (Pueraria lobata), 140-141
G

GABA (γ-aminobutyric acid), 42, 171
GABA receptors, 90-91
GABA transaminase, 102
galantamine, 152-159
adverse effects, 158-159
anti-inflammatory activity, 157
chemical structure of, 153
therapeutic use for Alzheimer’s disease, 155-157
pharmacodynamics, 155-156
pharmacokinetics, 154-155
galanthine, 153
Galanthus woronowi, 152
Galen, 84
γ-aminobutyric acid (GABA), 42
Ge Gen. See kudzu (Pueraria lobata)

GEM (Ginkgo Evaluation of Memory) study, 64
genistein, 140-142, 146
genistin, 140
geranial, 99
Gerard, John, 12, 70, 99, 125, 151-152
ginkgo (Ginkgo biloba)
   adverse effects, 65-66
   botany, 55
   constituents, 57-59
   historical use of, 53-54
   pharmacodynamics, 61-65
   pharmacokinetics, 59-61
   pharmacological perspective, 66
   popularity of, 53
   standardized extract, 58-59
   therapeutic uses, 55-57
Ginkgo Evaluation of Memory (GEM) study, 64
Ginkgoaceae, 53
ginkgolide B, 57-58
Ginkgophyla, 53
Giovanni Andrea (friar), 124
glia, 36
globus pallidus, 38
glutamic acid, 42
Glycininae, 139
glycitein, 142
glycosides in kudzu (Pueraria lobata), 140-143
government oversight of herbal supplements, lack of, 18-19
Graminae, 151
Greco-Roman era, herbal supplements in, 3, 11-13
growth of herbal supplement market, 18
Gymnosperm, 55
haemanthamine, 153
hal-life, 25
haloperidol, 46
hangover, effectiveness of kudzu
(Pueraria lobata) for, 145
harmaline, 164
harmalol, 164
harmane, 164
harmol, 164
Hatshepsut, 10
hepatotoxicity associated with
kava (Piper methysticum),
118-119
herbal supplement pharmacology
checklist, 28-32
heroin, 190
hippocampus, 37
Hippocrates, 11, 84
historical development of
pharmacology, 19-21
historical use of herbal
supplements
alchemy, 3-4, 13-15
Biblical mention of herbal
supplements, 1
chemistry, 4, 15-16
cocoa (Theobroma cacao),
175-177
coffee (Coffea arabica), 175-177
ey early documentation, 3, 9-11
ginkgo (Ginkgo biloba), 53-54
Greco-Roman era, 3, 11-13
kava (Piper methysticum),
109-110
kudzu (Pueraria lobata),
137-138
lavender (Lavandula
angustioliia), 123-124
laser balm (Melissa
officinalis), 97-98
passion flower (Passiflora
incarnata), 161-162
prehistoric evidence, 2, 8
St. John’s wort (Hypericum
perforatum), 67-69
tea (Camellia sinensis), 175-177
Valerian (Valeriana officinalis),
83-84
HMS Beagle, 109
HMS Endeavour, 109
Homer, 3, 9
homoorientin, 164-166
hydrophilic compounds, 24
hydroxyxlated phenylpropionic
acid, 101
hydroxyvalerenic acid, 89
hyoscyamine, 23
Hyoscyamus (apolinaris), 11-13
Hyoscymus niger, 23
hyperforin, 72-73, 76
hypericin, 71-72, 76
hypericins, 72
Hypericum attenuatum, 69
Hypericum maculatum, 69
Hypericum perforatum (St.
John’s wort)
adverse effects, 80-81
botany, 69-70
constituents, 71-74
historical use of, 67-69
pharmacodynamics, 75-80
pharmacokinetics, 74-75
pharmacological perspective,
81-82
therapeutic uses, 70-71
hypothalamus, 37
I

Ilex paraguariensis (maté), 177
The Iliad (Homer), 3, 9
in vitro studies, 27
in vivo studies, 27
inhibitory neurotransmitters, 40
insomnia, therapeutic use of
Valerian (Valeriana officinalis)
for, 93
ironwort (Sideritis heraclea), 13
isoflavones in kudzu (Pueraria lobata), 140-143
isoorientin, 164
isorhamnetin in ginkgo standardized extract, 58
isoschaftoside, 164-165
isovaleric acid, 87
isovitexin, 164-166

J-K

kaempferol
in ginkgo standardized extract, 58
in St. John's wort, 73, 77
kainic acid, 43
kava (Piper methysticum)
adverse effects, 118-120
botany, 110-111
constituents, 112
historical use of, 109-110
pharmacodynamics, 114-117
pharmacokinetics, 112-114
pharmacological perspective, 120-121
therapeutic uses, 111
kavain, 112-114
kavalactones, 112-119
ketamine, 43
kew. See ginkgo (Ginkgo biloba)
kudzu (Pueraria lobata)
adverse effects, 146-147
botany, 138-139
constituents, 140-141
historical use of, 137-138
pharmacodynamics, 143-146
pharmacokinetics, 141-143
pharmacological perspective, 147-148
therapeutic uses, 139-140

L

Labiatae, 98
Lamiaceae, 98, 124
Lan Mao, 54
Langley, John, 22
large scale clinical trials, 49
laudanum, 20
Lavandula angustifolia (lavender)
adverse effects, 134-135
botany, 124-125
constituents, 126-127
historical use of, 123-124
pharmacodynamics, 129-134
pharmacokinetics, 127-129
pharmacological perspective, 135-136
therapeutic uses, 125-126
Lavandula latifolia (spike lavender), 123-124
Lavandula stoechas (French lavender), 123-124
Lavandula x intermedia, 124
lavandulin, 125
lavender (Lavandula angustifolia)
adverse effects, 134-135
botany, 124-125
constituents, 126-127
historical use of, 123-124
pharmacodynamics, 129-134
pharmacokinetics, 127-129
pharmacological perspective, 135-136
therapeutic uses, 125-126

legislation
Dietary Supplement Health and Education Act of 1994, 18
Federal Food, Drug, and Cosmetic Act, 17
United States Pure Food and Drug Act, 17

Leguminosae, 139
lemon balm (Melissa officinalis)
adverse effects, 106
botany, 98
constituents, 99-100
historical use of, 97-98
pharmacodynamics, 102-105
pharmacokinetics, 100-102
pharmacological perspective, 106-107
therapeutic uses, 99
Li Shih-Chen, 54-55, 139

Librium® (chlordiazepoxide), 83
Liliaceae, 151
limbic system, 37-38
linalool, 126-131
linalyl acetate, 126-128, 131
linalys acetate, 126
Linnaeus, Carl, 97
lipid peroxidation, 104
lipophilic compounds, 24
Liu Wen-Tai, 54
liver toxicity associated with kava (Piper methysticum), 118-119
Logianaceae, 23
London Pharmacopeia, 125
lorazepam, 132
luteolin, 167-168
lycorine, 153-154, 157-158
Lycoris (spider lily), 153

M
Ma Huang, 190
maidenhair. See ginkgo (Ginkgo biloba)
major depression, 67
malaria, historical use of St. John’s wort for, 70
maltol, 164
Mandragora, 11
Manerix®, 75
MAO (monoamine oxidase) inhibition by kava, 116
marijuana, 191-192
maté (Ilex paraguariensis), 177
maypop. See passion flower (Passiflora incarnata)
Medicina Antiqua, 70
medulla, 37
megaleion, 9
Melissa officinalis (lemon balm), 11
adverse effects, 106
botany, 98
constituents, 99-100
historical use of, 97-98
pharmacodynamics, 102-105
pharmacokinetics, 100-102
pharmacological perspective, 106-107
therapeutic uses, 99
memory
scopolamine-induced memory impairment, 48
therapeutic use of ginkgo (ginkgo biloba) for, 64
Mendeleev, Dmitri, 16, 20
mendeleium, 16
mercuries (alchemy), 15
meta-coumaric acid, 101
methylxanthine alkaloids
  adverse effects, 186-187
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 178-180
methysticin, 112-114
Mithridates, King of Pontus, 12
mithridatum, 12, 124
Moclobemide, 75
The Mode of Action of Drugs on Cells (Clark), 24
Modern Herbal (Grieve), 125
monoamine oxidase (MAO)
  inhibition by kava, 116
Monocotyledonae, 151
monoterpenes
  in lemon balm (Melissa officinalis), 99
  in lavender (Lavandula angustiolia), 126
Morpheus, 20
morphine, 20, 70, 190
Morris water maze assay, 47
Muscari, presence in
  Neanderthal graves, 8
myrrh, 9-10

N
napthodianthrone, 72
Narcissus poeticus, 151
Narcissus pseudonarcissus (daffodil), 149-151
  adverse effects, 158-159
  botany, 151-152
constituents, 153-154
historical use of, 152
pharmacodynamics, 155-158
pharmacokinetics, 154-155
pharmacological perspective, 159
therapeutic uses, 152
Narcissus serotinus, 151
Nardostachys jatamansi (spikenard), 84
nardus. See lavender (Lavandula angustiolia)
National Formulary, 164
Natural History (Pliny), 97
Neanderthal use of herbal supplements, 2, 8
neopallium, 37
neral, 99
neurokinin, 158
neurons, 36
neuropharmacology
  behavioral assays, 45-48
  brain structure, 36-39
  chemical neurotransmission, 39-41
  clinical studies, 49-51
  definition of, 35
  neurotransmitter systems, 41-45
Neuropsychiatric Inventory and Alzheimer’s Disease Assessment Scale, 50
neurotransmission
  acetylcholine, 44
  adenosine, 43
  dopamine, 44
  explained, 39-41
  GABA (γ-aminobutyric acid), 42
  glutamic acid, 42
  neurotransmitter systems, 36, 41-45
  serotonin, 44
NF-kappaB inhibition by kava, 116
nitric oxide, 77
nitric oxide synthase, 77
norepinephrine, 75, 190
Norpramin® (desipramine), 116
Novum Organum, or New Method (Bacon), 15
nucleus accumbens, 37, 114

O
oleanolic acid, 99-101
1,8-cineole, 126-127
open-label clinical trials, 49
opium, 20-21
opium poppy, 190
orientin, 164-167
oxygen radicals, 185

P
PAF (platelet-activating factor), 63
paleopallium, 37
Papaver somniferum, 11, 20, 70, 190
Papaveraceae, 43
Paracelsus, 14, 20
Parkinson’s disease, 39
Passiflora incarnata (passion flower)
adverse effects, 173
botany, 162-163
constituents, 164-165
historical use of, 161-162
pharmacodynamics, 168-172
pharmacokinetics, 166-168
pharmacological perspective, 173-174
therapeutic uses, 163-164
Passiflora lutea, 162
Passifloraceae, 162
passion flower (Passiflora incarnata)
adverse effects, 173
botany, 162-163
constituents, 164-165
historical use of, 161-162
pharmacodynamics, 168-172
pharmacokinetics, 166-168
pharmacological perspective, 173-174
therapeutic uses, 163-164
passive diffusion, 25
Pen Ts’ao Kang Mu (Li Shih-Chen), 54
Peonia, 11
peptides, 158
Periodic Table of Elements, development of, 16, 20
pharmacodynamics
challenges of assessing herbal supplements, 27-28
of cocoa (Theobroma cacao), 184-186
of coffee (Coffea arabica), 184-186
of daffodil (Narcissus pseudonarcissus), 155-158
development of, 22-23
drug receptors, discovery of, 22-24
explained, 21-24
of ginkgo (Ginkgo biloba), 61-65
of kava (Piper methysticum), 114-117
of kudzu (Pueraria lobata), 143-146
of lavender (Lavandula angustiolia), 129-134
of lemon balm (Melissa officinalis), 102-105
of passion flower (Passiflora incarnata), 168-172
pharmacology checklist for herbal supplements, 28-32
of plant alkaloids, 192-193
of St. John’s wort (Hypericum perforatum), 75-80
of tea (Camellia sinensis), 184-186
of Valeriana officinalis (Valerian), 90-93
pharmacokinetics
bioavailability, 24-26
challenges of assessing herbal supplements, 27-28
of cocoa (Theobroma cacao), 182, 184
of coffee (Coffea arabica), 182-184
of daffodil (Narcissus pseudonarcissus), 154-155
explained, 24-27
of ginkgo (Ginkgo biloba), 59-61
half-life, 26
of kava (Piper methysticum), 112-114
of kudzu (Pueraria lobata), 141-143
of lavender (Lavandula angustiolia), 127-129
of lemon balm (Melissa officinalis), 100-102
of passion flower (Passiflora incarnata), 166-168
of plant alkaloids, 192-193
of tea (Camellia sinensis), 182-184
of Valeriana officinalis (Valerian), 88-90
pharmacology checklist for herbal supplements, 28-32
of St. John’s wort (Hypericum perforatum), 74-75
pharmacology checklist for herbal supplements, 28-32
phenobarbital, 43, 83
phosphodiesterase, 184
phytoestrogens, 141, 146
Piper methysticum (kava)
adverse effects, 118-120
botany, 110-111
constituents, 112
historical use of, 109-110
pharmacodynamics, 114-117
pharmacokinetics, 112-114
pharmacological perspective, 120-121
therapeutic uses, 111
Piper nigrum, 110
Piper wickmanni, 110
Piperaceae, 110
pipermethystine, 118
placebos, 51
platelet-activating factor (PAF), 63
Pliny, 68, 97, 152
Pliny the Elder, 3
plus maze test, 92
polyphenols, 181
pons, 37
postsynaptic neurons, 40
prefrontal cortex, 37
prehistoric evidence of herbal supplement use, 2, 8
presynaptic receptors, 40
primary motor area (cerebral cortex), 38
proteins
  beta amyloid, 47
  transporter proteins, 25-26
Psuedo-Apuleius, 13
psychiatric disorders, therapeutic
  use of ginkgo (Ginkgo biloba)
  for, 64
psychotherapeutics, challenges in
testing, 50-51
Pueraria chinensis, 139
Pueraria lobata (kudzu)
  adverse effects, 146-147
  botany, 138-139
  constituents, 140-141
  historical use of, 137-138
  pharmacodynamics, 143-146
  pharmacokinetics, 141-143
  pharmacological perspective, 147-148
  therapeutic uses, 139-140
Pueraria montana, 139
puerarin, 140-146
purple passion flower. See
  passion flower (Passiflora
  incarnata)
putamen, 38
pyriform cortex, 37

Q-R
quercetin
  in ginkgo standardized
  extract, 58
  in St. John’s wort, 73, 77
receptors, discovery of, 22-24
regulation of herbal
  supplements, lack of, 18-19
Rhazes, 14
rivastigmine, 156
Rome, historical use of herbal
  supplements, 3, 11-13
rosmarinic acid, 99-103
rosuvastatin, interaction with
  lemon balm (Melissa
  officinalis), 101
Rubiaceae, 178
S
salicin, purification of, 21
salicylic acid, 21
Salix spp., 21
salts (alchemy), 15
The Sceptical Chymist
  (Boyle), 15
schaftoside, 164-165
sciatica, historical use of St.
  John’s wort for, 70
scopolamine-induced memory
  impairment, 48
Senecio, presence in
  Neanderthal graves, 8
sensory cortex, 38
septum, 37
serotonin, 36, 42-44, 75
sertraline, 79
Sertturner, Freidrich, 20
sesquiterpenes, 87-90
Shen Nong Ben Cao Jing, 54
side effects. See adverse effects
Sideritis heraclea (ironwort), 13
sigma receptors, 77
silexan, 132
6,7-epoxy-linalool, 128
Solanaceae, 10
spider lily (Lycoris), 153
spike lavender (Lavandula
  latifolia), 123-124
spikenard (Nardostachys
  jatamansi), 84
squill (Urgenia maritima), 13
St. John’s wort (Hypericum perforatum), 74-75
  adverse effects, 80-81
  botany, 69-70
  constituents, 71-74
  historical use of, 67-69
  pharmacodynamics, 75-80
  pharmacokinetics, 74
  pharmacological perspective, 81-82
  therapeutic uses, 70-71
St. Peter’s wort (Ascyrum), 70
standardized extract of ginkgo (Ginkgo biloba), 58
Strychnos, 23
substantia nigra, 38
sulfsurs (alchemy), 15
swertisin, 164
swertismarin, 165
symptom scales, 50
synapses, 36
synaptic cleft, 36

t1/2 (half life), 26
tacrine, 156
tannins in St. John’s wort, 73
tea (Camellia sinensis)
  adverse effects, 186-187
  botany, 177-178
  constituents, 180-182
  historical use of, 175-177
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 178-180
Theophrastus, 9, 97, 151
theobromine, 180-181
  adverse effects, 186-187
  pharmacodynamics, 184-186
  pharmacokinetics, 182-184
  pharmacological perspective, 187-188
  therapeutic uses, 179
thiopental, 83
Tincture of Opium, 20
transient receptor potential channels (TRPC), 76
transmitters
  acetylcholine, 44
  adenosine, 43
  dopamine, 44
  explained, 39-41
  GABA (γ-aminobutyric acid), 42
glutamic acid, 42
neurotransmission, 40
serotonin, 44
transporter proteins, 25-26
trigonelline, 182
triterpenes in lemon balm
(Melissa officinalis), 99
TRPC (transient receptor
potential channels), 76

U
United States Food and Drug
Administration. See FDA (Food
and Drug Administration)
United States National
Formulary, 164
United States Pure Food and
Drug Act, 17
Urgenia maritima (squill), 13
ursolic acid, 99-101

V
valerophutiates, 87-90
valerenic acid, 88-92
Valerian (Valeriana officinalis)
adverse effects, 93-94
botany, 84-85
constituents, 86-88
historical use of, 83-84
pharmacodynamics, 90-93
pharmacokinetics, 88-90
pharmacological perspective,
94-95
therapeutic uses, 85-86
valerian epoxy triesters, 87
Valeriana, 11
Valeriana celtica (French
spikenard), 84
Valeriana ciliata, 85
Valeriana officinalis (Valerian)
adverse effects, 93-94
botany, 84-85
constituents, 86-88
historical use of, 83-84
pharmacodynamics, 90-93
pharmacokinetics, 88-90
pharmacological perspective,
94-95
therapeutic uses, 85-86
Valeriana pauciflora, 85
Valeriana septentrionalis, 85
Valeriana uliginosa, 85
Valerianaceae, 84
Valium® (diazepam), 43, 83
vesicles, 40
vestibular nuclei, 38
vitexin, 164-166

W-X-Y-Z
wild apricot. See passion flower
(Passiflora incarnata)
willow bark extract, 21
yangonin, 112-114
yarrow (Achillea millefolium)
presence in Neanderthal graves,
2, 8
use in Greco-Roman era, 3
yellow passion flower (Passiflora
lutea), 162
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