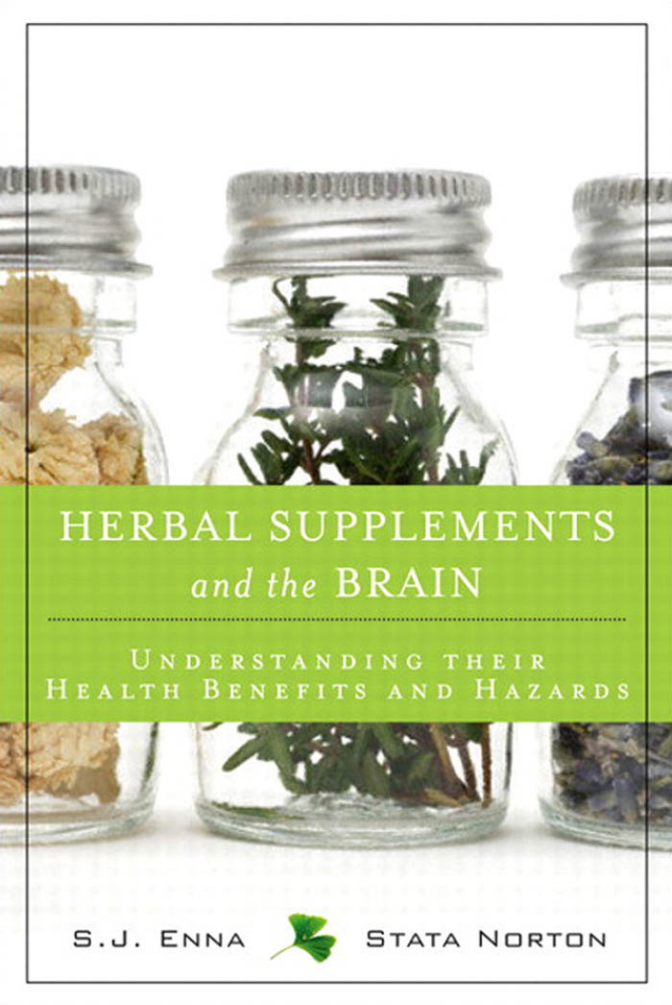
HERBAL SUPPLEMENTS
and the BRAIN
UNDERSTANDING THEIR
HEALTH BENEFITS AND HAZARDS
S.J. ENNA
STATA NORTON

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."

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"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."

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—**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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Herbal Supplements and the Brain

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Herbal Supplements and the Brain

Understanding Their Health Benefits and Hazards

S. J. Enna
Stata Norton

Illustrated by Kevin S. Smith

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About the Authors

A Kansas City native, **S. J. Enna** received his undergraduate education at Rockhurst University and his M.S. and Ph.D. degrees in pharmacology from the University of Missouri. Following postdoctoral work at the University of Texas Southwestern Medical School in Dallas, F. Hoffmann-LaRoche in Basel, Switzerland, and Johns Hopkins University Medical School, Dr. Enna joined the faculty at the University of Texas Medical School in Houston in the departments of Pharmacology and of Neurobiology and Anatomy. In 1986, Dr. Enna was appointed Scientific Director of Nova Pharmaceutical Corporation in Baltimore. At this time, he also held appointments as a Lecturer in Neuroscience at Johns Hopkins Medical School and Adjunct Professor of Pharmacology at Tulane Medical School in New Orleans. Dr. Enna returned to Kansas City in 1992 as Professor and Chair of Pharmacology at the University of Kansas Medical Center, where he is currently Associate Dean for Research and Graduate Education, and Professor of Pharmacology and of Physiology. Dr. Enna has published nearly 300 research reports, reviews, and book chapters describing his research, and has edited or coedited 30 books on various subjects relating to neuropharmacology. For decades, he has served as a scientific consultant for most of the major pharmaceutical companies and as a board member on government panels and private research foundations. He has been appointed to the editorial boards of numerous pharmacology journals and has served as editor of leading journals in the field, including the *Journal of Pharmacology and Experimental Therapeutics.*

At present, Dr. Enna is editor of *Biochemical Pharmacology* and *Pharmacology and Therapeutics*, coeditor of *Current Protocols in Pharmacology*, and series editor of *Advances in Pharmacology.* Dr. Enna has held many elective offices in professional societies, including the presidency of the American Society for Pharmacology and Experimental Therapeutics. Currently, he is Secretary-General of the International Union of Basic and Clinical Pharmacology. He has received numerous awards in recognition of his contributions to the discipline of pharmacology. Among these are two Research Career

Development Awards from the National Institutes of Health, the John Jacob Abel and Torald Sollmann Awards from the American Society for Pharmacology and Experimental Therapeutics, the Daniel H. Efron Award from the American College of Neuorpsychopharmacology, and the PhRMA Foundation Excellence Award from the Pharmaceutical Manufacturer's Association Foundation. Dr. Enna is internationally recognized for his research in neuropharmacology, especially his contributions in characterizing the biochemical and pharmacological properties of neurotransmitter receptors in general, and the γ-aminobutyric acid (GABA) system in particular.

Dr. Stata Norton received her B.S. degree in Biology from the University of Connecticut, Storrs, her Master's degree in Zoology from Columbia University in New York, and her Ph.D. degree in Zoology and Physiological Chemistry from the University of Wisconsin in Madison. After working for over a decade as a neuropharmacologist at the Wellcome Research Laboratories in Tuckahoe, New York, in 1962, she accepted a faculty appointment in Department of Pharmacology, Toxicology, and Therapeutics at the University of Kansas Medical School in Kansas City. While at the University of Kansas, she also served as Professor of Dietetics and Nutrition, Dean of the School of Allied Health, and Professor at the Institute for Cell Biology in Valencia, Spain. Since 1990, she has been Emeritus Professor of Pharmacology at the University of Kansas Medical School.

Dr. Norton was the recipient of a Research Scientist Award from the National Institute of Mental Health and was elected to Outstanding Educators of America in 1975. She served on the Editorial Advisory boards for *Psychopharmacology, Neurotoxicology,* and *Toxicology and Industrial Health.* She was President of the Central States Chapter of the Society of Toxicology and a member of the Preclinical Psychopharmacology Study Section of the National Institute of Mental Health. She has published more than 150 scientific research articles and reviews in scientific journals and books. Her main research interests are the development of quantitative methods for analyzing animal behavior and the characterization of the effects of chemicals on behavior. For more than two decades, she authored a major review on the toxic effects of plants for the reference work *Toxicology: The Basic Science of Poisons.*

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.

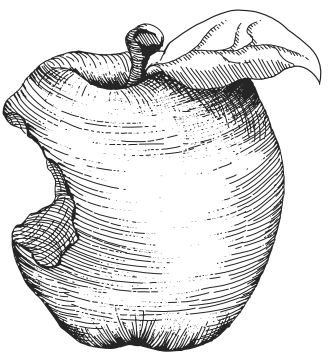
Written for the nonscientist, the book is informally divided into two parts. The first section, chapters 1–4, provides an historical perspective on the use of plant products to modify central nervous system function and on the development of the techniques employed for drug discovery. Included is a discussion 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.

1

The Gifts of Eden



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.[1] 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,[2] 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.[3]

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.[4] 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.[5] 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.[6] 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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