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Pharmacological Characterization of Nutraceuticals

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CHAPTER 8

Pharmacological Characterization of Nutraceuticals

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DEFINITION OF PHARMACOLOGICAL CHARACTERIZATION

The pharmacological characterization of a nutraceutical is simply the determination of its efficacy and safety. Currently, many nutraceuticals (e.g., botanicals) do not require efficacy and safety testing before marketing. They are regulated by the Dietary Supplement Health and Education Act of 1994, which considers many nutraceuticals as food items [Dietary Supplement Health and Education Act 1994]. However, there is a concern that many nutraceuticals have pharmacological activity that can endanger the public health and that certain nutraceuticals (e.g., botanicals) should be regulated similarly to prescription drugs [Morrow et al. 2005]. Therefore, future marketing of nutraceuticals may require more rigorous testing of safety and efficacy before marketing.

In fact, as of June 22, 2007, the FDA developed a current good manufacturing practice requirement for dietary supplements that obligates manufacturers to evaluate
the composition, identity, quality, and strength of their marketed products [Food and Drug Administration 2007]. With future increased regulation of nutraceuticals on the horizon, the current pharmacological characterization of drugs will be discussed. At this point, it would be helpful to briefly review the drug development and testing process in the United States. The following is a simplified drug review process [Food and Drug Administration 2002; Berkowitz 2007]:

1. Preclinical testing: in vitro studies, animal models
2. Phase I: 20–80 human subjects, safety, pharmacokinetics
3. Phase II: 36–300 human subjects, efficacy
4. Phase III: 300–3,000 human subjects, efficacy, double-blind studies
5. Phase IV: post-marketing surveillance

The drug review process is roughly divided into preclinical and clinical testing, and, as noted above, preclinical is primarily in vitro and animal studies, whereas clinical are human studies.

**PRECLINICAL**

**Pharmacological Profile Tests**

Preclinical testing involves pharmacological profile tests for drugs, and it can be further divided into the following [Berkowitz 2007]:

1. Molecular: receptor binding, enzyme inhibition
2. Cellular: cell cultures, isolated tissues
3. Disease models: pain, seizures

Initial pharmacological characterization of a nutraceutical would take place preclinically in in vitro studies and animals to determine efficacy and safety. Table 8.1 provides some examples of preclinical pharmacological characterizations of nutraceuticals.

<table>
<thead>
<tr>
<th>Nutraceutical</th>
<th>In Vitro/In Vivo</th>
<th>Pharmacology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort</td>
<td>Rat brain homogenates</td>
<td>Inhibition of monoamine oxidase</td>
<td>Bladt and Wagner 1994</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Rat</td>
<td>Antidepressant</td>
<td>De Vry et al. 1999</td>
</tr>
<tr>
<td>Cat’s claw</td>
<td>Salmonella typhimurium</td>
<td>Antimutagenic</td>
<td>Rizzi et al. 1993</td>
</tr>
<tr>
<td>Devil’s claw</td>
<td>Rat</td>
<td>Anti-inflammatory</td>
<td>Andersen et al. 2004</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Rat</td>
<td>Immunostimulation</td>
<td>Cundell et al. 2003</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Rat leukocytes</td>
<td>COX inhibition</td>
<td>Capasso 1986</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Rat</td>
<td>Cognition Improved</td>
<td>Winter 1998</td>
</tr>
<tr>
<td>Kava</td>
<td>Chick</td>
<td>Anxiolytic</td>
<td>Feltenstein et al. 2003</td>
</tr>
<tr>
<td>Glucosamine and chondroitin</td>
<td>Horse</td>
<td>Stride Improvement</td>
<td>Forsyth, Brigden, and Northrop 2006</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Rat</td>
<td>Antioxidant</td>
<td>Augusti et al. 2007</td>
</tr>
</tbody>
</table>

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Safety Tests and Toxicology Tests

Preclinical safety testing assesses the potential toxicity of a drug in *in vitro* and animal studies [Food and Drug Administration 1985; Berkowitz 2007]. Below is a listing and a short commentary on the type of safety tests required by the FDA:

1. Pharmacology studies: determine ED$_{50}$
2. Acute toxicity studies: determine LD$_{50}$
3. Multidose toxicity studies
   a. Subchronic toxicity: duration of one to three months
   b. Chronic toxicity: duration of six months
   c. Carcinogenicity: duration of two years
4. Special toxicity studies: route of administration
5. Reproduction studies: birth defects
6. Mutagenicity studies: Ames test
7. Pharmacokinetics studies: ADME

EVALUATION IN HUMANS

Clinical studies involve human subjects, and they are divided into four phases: Phase I, Phase II, Phase III, and Phase IV. The goal of these clinical trials is to validate that the drug demonstrates efficacy and safety before it is marketed. As discussed previously, the preclinical testing would have rejected those chemical entities that did not demonstrate efficacy and/or caused unacceptable toxicity, such as a poor safety profile.

Because the test subjects for clinical studies are human beings, the highest ethical and moral regard for their safety must be paramount. Therefore, two important safeguards are inherent to clinical trials: institutional review boards (IRB) and informed consent. The primary function of institutional review boards is to review proposed clinical research procedures, ensure that the proposed research is going to be conducted according to proper procedures, including institutional, local, state, and federal regulations. They are made up of individuals who have no conflict of interest with the clinical research that is being conducted by the institution (i.e., a drug company). It is usually made up of five or more members of the institution with different backgrounds and at least one outside person. Each participant in the clinical study must be given informed consent, and essential components include the following: a description of the research to be conducted, risks/benefits, and the ability to withdraw from the trial for any reason [Food and Drug Administration 1997].

There are several important parameters to be carefully considered when conducting clinical research to ensure the highest scientific standards:

1. Design and analysis considerations
2. Selection of subjects
Important design and analysis considerations include the following: the appropriate use of statistics, careful planning of the clinical trials, and rationale for the length of the clinical trials. The selection of human subjects should involve a wide variety of parameters, such as age, sex, and ethnicity. The numbers of patients in the clinical trials are important, especially with regard to statistical considerations. Randomization of patients increases the confidence in the conclusions drawn from the study [Edwards 2001]. Study control is the use of a placebo or, because of the nature of the disease, the use of a positive control is warranted. To enhance the validity of the study, patient compliance must be diligently documented. An important dose consideration is the effective range of the drug (i.e., lowest and highest doses). The pharmacokinetics of the investigational drug must be ascertained (e.g., ADME). This topic will be discussed in additional detail in the next chapter. Tests for safety involve the appropriate laboratory tests (e.g., blood urea nitrogen) to monitor the health of the patient [Food and Drug Administration 1997].

Before a Phase I clinical trial can start, the drug company must submit a Notice of Claimed Investigational Exemption for a New Drug (IND) to the FDA. The IND must include the following information:

1. Drug source and composition
2. Information on manufacturing and chemistry
3. Animal studies data
4. Clinical trial plans and protocols
5. Credentials of the physicians conducting the trials
6. Key drug information given to investigators and their institutional review boards

It can take four to six years to collect enough preclinical data to submit an IND.

**Phase I**

In Phase I, about 20–80 healthy human subjects are involved. An important goal of this phase is to determine the maximum tolerated dose with minimal toxicity. An exception would be the use of certain drugs (e.g., antineoplastics), which are very toxic; patients with the disease being studied would be involved at this point rather than healthy volunteers. Many pharmacokinetic parameters are determined in this phase, such as absorption and metabolites. These trials are nonblinded, which means that both the investigator and patient know what is being given.
Phase II

In Phase II, about 36–300 human subjects with the disease are studied for efficacy of the investigational drug. These trials are often single blinded, meaning that the investigator knows which treatment is used, with a placebo control and a positive control (i.e., an approved active drug).

Phase III

In Phase III, 300–3,000 patients with the disease being studied are given the investigational drug. With data from Phases I and II, this trial is able to minimize errors from placebo effects, disease variability, etc. This trial is double blinded, i.e., both the investigator and patient do not know which treatment is being given, with placebo, positive control, and crossover techniques. At this point, a new drug application can be submitted to the FDA if the data from Phase III demonstrates safety and efficacy. Vast amounts of preclinical and clinical data are submitted to the FDA.

Phase IV

Phase IV can begin once the drug is approved for marketing. This phase is primarily concerned with capturing toxicities not observed in the previous phases because of the lower number of human subjects and chronic dosing [FDA 1997; Berkowitz 2007]. Table 8.2 provides some examples of nutraceuticals that have undergone clinical trials.

Table 8.2 Clinical Trials with Nutraceuticals

<table>
<thead>
<tr>
<th>Nutraceutical</th>
<th>Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John's Wort</td>
<td>Treatment of depression</td>
<td>Gastpar, Singer, and Zeller 2006</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Treatment of vasomotor symptoms</td>
<td>Newton et al. 2006</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>Treatment of knee osteoarthritis</td>
<td>Mazieres et al. 2007</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Reduce polysialic acid</td>
<td>Bunker et al. 2007</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Treatment of dementia</td>
<td>Scripnikov, Khomenko, and Napryeyenko 2007</td>
</tr>
<tr>
<td>Cat's claw</td>
<td>Treatment of rheumatoid arthritis</td>
<td>Mur et al. 2002</td>
</tr>
<tr>
<td>Devil's claw</td>
<td>Treatment of back pain</td>
<td>Laudahn and Walper 2001</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Bioavailability</td>
<td>Woelkart et al. 2006</td>
</tr>
<tr>
<td>CoQ_{10}</td>
<td>Bioavailability</td>
<td>Nuku et al. 2007</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Pharmacokinetics</td>
<td>Boocock et al. 2007</td>
</tr>
</tbody>
</table>
REFERENCES


