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Review

Cross matching observations on toxicological and clinical data for the assessment of tolerability and safety of *Ginkgo biloba* leaf extract

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ABSTRACT

Ginkgo biloba is one of the most widely used herbal remedies in Europe and the US. It may be purchased in different types of formulations, but most of the clinical studies have been performed with the controlled *G. biloba* extract EGb761®. Indications include Alzheimers disease, cardiovascular disease, dementia, memory loss, and cerebral ischemia. The pharmacological modes of action cover antioxidant effects, radical scavenging, inhibition of platelet activating factor, alterations in membrane fluidity (signal transduction), and inhibition of glucocorticoid synthesis. Due to the widespread and long-term use of *G. biloba* – about a million doses of EGb761® are sold per day – tolerability and safety are a crucial issue. Based on broad and long-term clinical use of *G. biloba* extracts, it is regarded as well tolerated in man.

Cross matching, a tool we introduced, combines different fields of knowledge and types of data to a consolidated result. In this article, we combine toxicological and clinical data and utilize other sources of information to assess tolerability and safety of *G. biloba*. It is well known that because of biological differences between animals and man or even between animal species, animal experiments do not necessarily mimic the effects in humans. Therefore, for adequate risk assessment, the relevance of non-clinical toxicological findings should be correlated with human data. The cross matching of toxicological data and results from clinical studies is possible because many toxicological and clinical studies are available on *G. biloba*. We give an in depth analysis of the modes of action in animals and describe toxicological studies with regard to metabolism, pharmacokinetics, genotoxicity, as well as carcinogenicity (e.g., the Technical Report TR 578 of the US National Toxicology Program). In addition, 75 clinical trials with high methodological quality are summarized. They included a total of 7115 patients treated with *G. biloba*. Based on this extensive amount of information, the broad variety of investigations, and their accordance we conclude that *G. biloba* extract is well tolerated and safe for humans.

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Contents

Abbreviations: CYP, cytochrome P-450; GSH-transferase, glutathione-S-transferase; UDP-glucuronosyltransferase, uridine 5′-diphospho-glucuronosyltransferase; EGb761®, *Ginkgo biloba* extract, CAS 122933-57-7; AhR, aryl hydrocarbon receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor; ADME, absorption, distribution, metabolism, excretion.

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1. Introduction

1.1. Importance of Ginkgo biloba extract

Extracts from *Ginkgo biloba* leaves have a long history, and today *G. biloba* is one of the most commonly used herbal medicinal products in Europe and in the US (EMA/HMPC/321095/2012, 2014; Saper, 2014). The extract taken most is the standardized extract EGb761®. *G. biloba* leaf extract is available as film-coated tablets, oral liquids, and injectable solutions. In Europe *G. biloba* extract is primarily regulated as herbal medicine, but in the US as a dietary supplement sold with health claims. *G. biloba* extract is used for diseases such as Alzheimer's disease, cardiovascular disease, dementia, memory loss, and cerebral ischemia (Pereira et al., 2013; Diamond and Bailey, 2013; Herrschaft et al., 2012). The pharmacological modes of action include antioxidant effects, radical scavenging, inhibition of platelet activating factor, alterations in membrane fluidity (signal transduction), and inhibition of glucocorticoid synthesis (Pereira et al., 2013; Diamond and Bailey, 2013).

1.2. Components of G. biloba

A plant extract contains several chemical constituent types. Each component may possess different modes of action related to pharmacological and toxicological effects. Therefore, when assessing the risk of *G. biloba* leaf extract to humans a separate analysis of

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