INVESTIGATION OF THE LYMPHATIC TRANSPORT OF SOLID-LIPID CURCUMIN PARTICLES (LONGVIDA®) IN COMPARISON TO CURCUMIN EXTRACT IN RATS

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INTRODUCTION

It is well known that curcumin has a low, apparent bioavailability in humans mainly due to its instability in physiological pH-conditions in the small intestine and extensive first-pass metabolism.[1] The majority of previous human studies indicate that a major part of curcumin appears in blood as its metabolite curcumin-glucuronide. Only a minor part is detected in plasma as unglucuronidated curcumin. The pharmacokinetic profile provides a hypothesis for the lack of efficacy observed in many clinical studies, in which even high doses of curcumin administered orally yielded negligible unconjugated curcumin plasma levels.[2,3,4] Further, in recently published in vivo studies efficacy of curcumin is most likely correlated with circulating levels of free (unglucuronidated) curcumin.[5,6,7] In a small human pilot trial, it could be shown that curcumin from the solid-lipid curcumin particles (Longvida®) yields substantially higher levels of free circulating curcumin when compared to conventional curcumin extracts.[8] To further examine these encouraging results, a pharmacokinetic study of curcumin, with special emphasis laid on lymphatic absorption either from standard 95% curcumin extract or from solid-lipid curcumin particles (Longvida®) was investigated in rats.

OBJECTIVE

The objective of the study was to investigate whether the previously observed, a substantial increase of free (unglucuronidated) curcumin blood concentrations after administration of solid-lipid curcumin particles (Longvida®) when compared to standard 95% curcumin extract, could be explained by an increased lymphatic uptake and transport of curcumin.

METHODOLOGY

Following previously published designs [9,10] five rats received a single oral dose of 75 mg curcumin/kg body weight as either standard 95% curcumin extract or Longvida®. Prior to treatment, the rats were anaesthetized followed by a surgical intervention to cannulate the mesenteric lymph duct (for lymph collection) and the carotid artery (for blood collection). The cannulas were externalized and the rats were allowed to recover for 24 hours. Thereafter, either standard 95% curcumin extract or Longvida® were administered via gavage. Blood (0.25 ml) was sampled prior to and at 0.5, 1.0, 2.0, 3.0 and 5.0 hours after administration into vials coated with EDTA. Blood samples were centrifuged to obtain plasma and stored at <-30 °C until analysis. Mesenteric lymph (0.25 ml) was collected prior to and 1 and 5 hours after administration into vials coated with EDTA and stored at <-30 °C until analysis. Analysis of curcumin and glucuronidated curcumin was performed by HPLC with UV-detection coupled to MS according to published methods [2,4]. The analytical method was validated including stability of curcumin and curcumin glucuronide in blood/plasma and lymphatic fluid. The Limit of Determination (LOD) was set to 2.5 ng/ml biological fluid.

RESULTS/DISCUSSION

About 10-fold higher lymphatic concentrations of free (unglucuronidated) curcumin were observed after administration of Longvida® when compared to standard 95% curcumin extract.

It is well known that curcumin undergoes extensive first-pass metabolism yielding high amounts of curcumin-glucuronide in the blood after oral administration. The lymphatic transport of curcumin after oral administration circumvents the liver and the first-pass metabolism.

An increased curcumin transport through the lymphatic system prompts the delivery of higher amounts of free (unglucuronidated) curcumin into the blood stream.

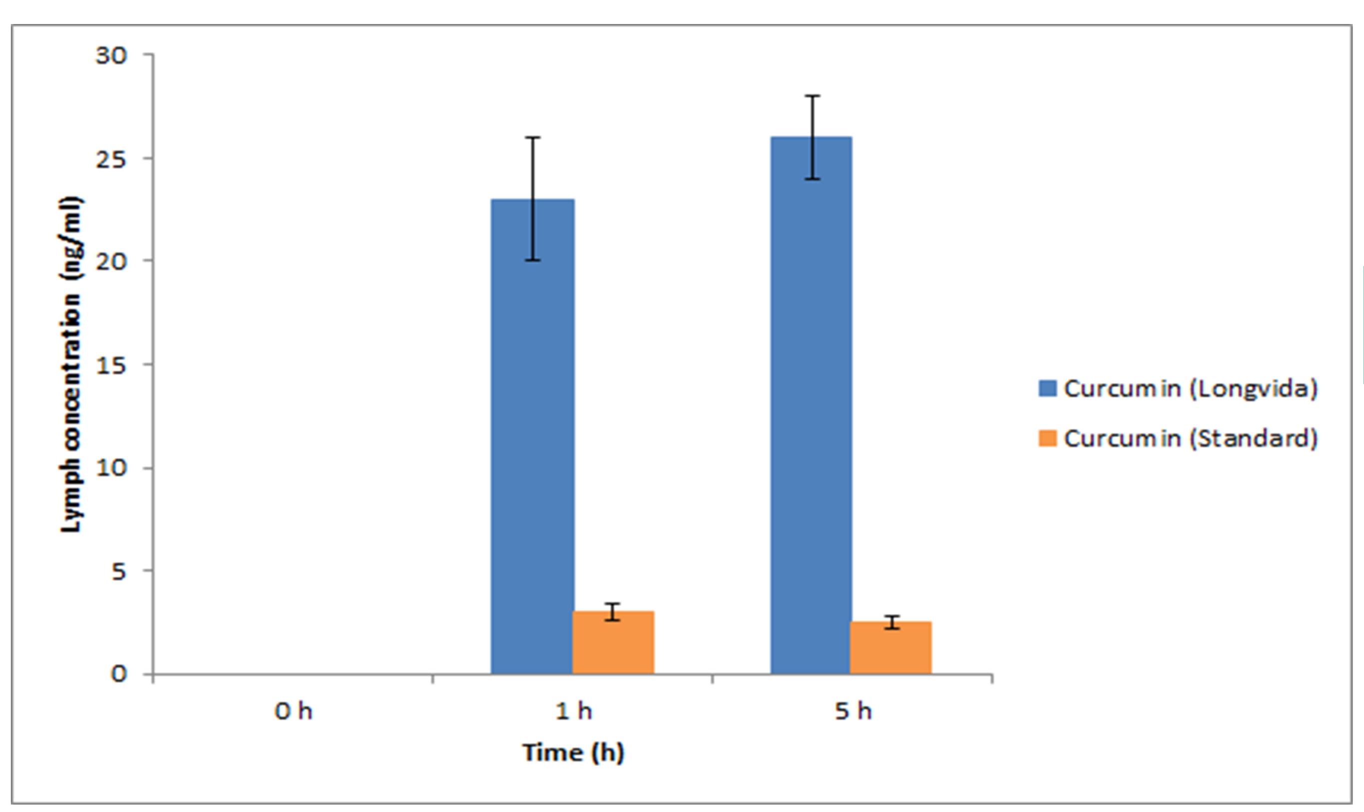

Figure 1, Lymphatic fluid concentrations of free (unglucuronidated) curcumin (mean values ± s.d.; n=5)

RESULTS/DISCUSSION

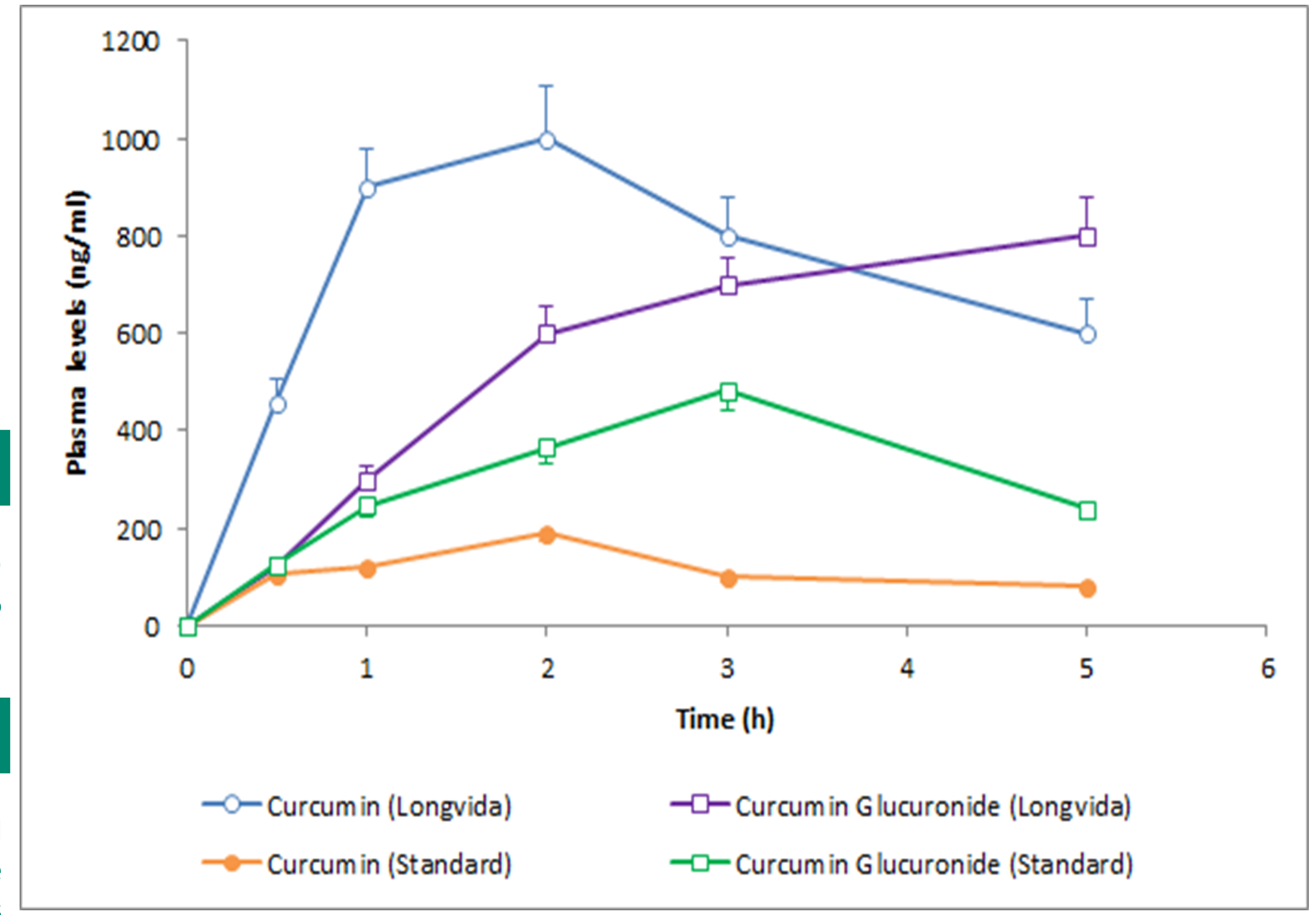

Figure 2, Plasma concentrations of free and glucuronidated curcumin (mean values ± s.d.; n=5)

The pharmacokinetic test results reported in Figure 2 suggest approximatively 5-times higher relative bioavailability of free (unglucuronidated) curcumin in the plasma after oral administration of Longvida® in comparison to standard 95% curcumin extract.

In addition, the ratio of free to glucuronidated curcumin indicates that compared to standard 95% curcumin extract a substantially higher fraction of free (unglucuronidated) curcumin reaches the blood stream after administration of Longvida®.

The high amount of curcumin found in the lymphatic fluid after treatment with Longvida® serves as explanation for its increased bioavailability when compared to standard 95% curcumin extract.

CONCLUSION

Study results strongly indicate that curcumin, after oral administration in the form of solid-lipid curcumin particles (Longvida®), circumvents the liver and the first-pass metabolism with lymphatic uptake; yielding substantially higher concentrations of circulating free curcumin compared to conventional standard 95% curcumin extract. Interestingly curcumin, but not its metabolite (curcumin glucuronide) ,follows the Lipinski's five rules for biological activities.[11] Recently, the central nervous system lymphatic system has been discovered and reported by scientists at University of Virginia.[12] In summary, these findings along with the ability of unconjugated curcumin to cross the blood brain barrier with enhanced lymphatic concentrations of free curcumin after oral administration of solid-lipid curcumin particles (Longvida®), could support previously reported higher concentrations of curcumin, but not its metabolite (curcumin glucuronide) in the brain and central nervous system.[5] These results add further support of efficacy associated with curcumin when consumed as solid-lipid curcumin particles (Longvida®).

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