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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MANGALA P. BAJPAI

Appeal 2018-002926
Application 12/054,129
Technology Center 1600

Before JEFFREY N. FREDMAN, ULRIKE W. JENKS, and RICHARD J. SMITH, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method for identifying medicinally active chemical entities. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Biological Life, Inc. (*see* App. Br. 3).
[2] We have considered and refer to the Specification of Mar. 24, 2008 ("Spec."); Final Action of Dec. 20, 2016 ("Final Act."); Appeal Brief of Oct. 18, 2017 ("App. Br."); Examiner's Answer of Nov. 29, 2017 ("Ans."); and Reply Brief of Jan. 26, 2018 ("Reply Br.").

Statement of the Case

Background

"This invention relates generally to methods of drug discovery and development, and more specifically concerns such a method which is substantially faster in identifying safe and effective drugs produced from ethnobotanical substances than existing methods" (Spec. 1:8–11).

The Claims

Claims 1–8, 12–24 and 28–42 are on appeal. Independent claim 1 is representative and reads as follows:

> 1. A method for identifying medicinally active chemical entities in ethnobotanical substances, comprising the steps of:
>
> (1) providing an ethnobotanical natural substance occurring naturally in nature, the ethnobotanical substance comprising an existing land or marine plant source identified as having an active agent associated with a medicinal effect on humans, wherein the land or marine plant source consists of roots or fruits or seeds or bark or leaves;
>
> (2) performing an *in-vitro* assay with the ethnobotanical substance with one or more of the following: (a) human intestinal preparations and (b) human liver preparations, thereby producing an array of human chemical entities;
>
> (3) performing an *in-vitro* assay of said ethnobotanical substance using one or more of the following: (a) animal intestinal preparations and (b) animal liver preparations from at least one selected animal species to produce an array of animal chemical entities;
>
> (4) comparing the array of human chemical entities with the array of animal chemical entities;
>
> (5) determining any matches between the human chemical entities in the array of human chemical entities and the animal chemical entities in the array of animal chemical entities to identify a matched animal species;
>
> (6) performing an *in-vivo* dosing of the ethnobotanical substance with the matched animal species;

> (7) obtaining a biological fluid sample from the matched animal species following the *in-vivo* dosing;
>
> (8) performing an analysis of the biological fluid sample from the matched animal species to determine the presence of chemical entities in the biological fluid sample; and
>
> (9) comparing the chemical entities in the biological fluid sample with the human chemical entities from the *in-vitro* assay and determining any matches between the chemical entities in the biological fluid sample with the human chemical entities from the *in-vitro* assay, wherein the matched chemical entities are identified as potentially medicinally active chemical entities.

The Issues

A. The Examiner rejected claims 1–7, 12, 13, 15, 17–23, 28, 29, 31, 33–39, and 41 under 35 U.S.C. § 103(a) as obvious over Ireson,[3] Chattopadhyay,[4] and Gilbert[5] (Ans. 3–8).

B. The Examiner rejected claims 1–8, 12, 13–15, 17–24, 28–31, and 33–41 under 35 U.S.C. § 103(a) over Ireson, Chattopadhyay, Gilbert, and Lu[6] (Ans. 8–9).

C. The Examiner rejected claims 1–7, 12, 13, 15–23, 28, 29, 31–39, 41, and 42 under 35 U.S.C. § 103(a) over Ireson, Chattopadhyay, Gilbert, and Barnes[7] (Ans. 10–11).

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[3] Ireson et al., *Characterization of Metabolites of the Chemopreventive Agent Curcumin in Human and Rat Hepatocytes and in the Rat in Vivo, and Evaluation of Their Ability to Inhibit Phorbol Ester-induced Prostaglandin E_2 Production*, 61 CANCER RES. 1058–1064 (2001).

[4] Chattopadhyay et al., *Turmeric and curcumin: Biological actions and medicinal applications*, 87 CURRENT SCIENCE 44–53 (2004).

[5] Gilbert et al., *Synergy in Plant Medicines*, 10 CURRENT MEDICINAL CHEMISTRY 13–20 (2003).

[6] Lu et al., *Comparison of Intrinsic Clearance in Liver Microsomes and Hepatocytes from Rats and Humans: Evaluation of Free Fraction and Uptake in Hepatocytes*, 34 DRUG METABOLISM AND DISPOSITION 1600–05 (2006).

A. 35 U.S.C. § 103(a) over Ireson, Chattopadhyay, and Gilbert

The Examiner states that Ireson teaches, *inter alia*, "a method comprising the steps of: providing the naturally occurring ethnobotanical substance curcumin associated with anti-inflammatory and cancer chemopreventative activities, which reads on in part on" claim 1 along with the in vitro and in vivo assay steps and comparisons required by claim 1 (Ans. 6).

The Examiner acknowledges that Ireson "does not teach a method wherein the naturally occurring ethnobotanical substance comprising an existing land plant source identified as having a medicinal effect on humans consists of roots, fruits, seeds, bark or leaves" as required by claims 1, 17, and 33 or the use of "a plurality of animal species" as required by claims 3, 19, and 35 (Ans. 5–6).

The Examiner finds Chattopadhyay teaches turmeric, a powdered rhizome (root) "is an unrefined, unpurified medicinal plant which has an extensive history in Traditional Indian and Chinese medicine and comprises many different compounds, including curcumin and that both curcumin and turmeric have the potential for the development of modern medicine for the treatment of various diseases" (Ans. 6). The Examiner finds Gilbert teaches

> plant derived medicines depend on active principles that in many cases require adjuvant substances in the plant which enhance the activity of the components responsible for the effect and in some cases the isolated substance is often less active by itself than when retained in the mixture present in the plant itself.

(Ans. 6).

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[7] Barnes et al., *Applications of LC-MS in the study of the uptake, distribution, metabolism and excretion of bioactive polyphenols from dietary supplements*, 78 LIFE SCIENCES 2054–59 (2006).

The Examiner finds it obvious to use Chattopadhyay's medicinal root turmeric in the place of Ireson's purified curcumin based on Gilbert's teaching that "plant derived medicines may be less active when in isolated (refined, purified) form due to the loss of adjuvant enhancing substance" (Ans. 7). The Examiner finds it obvious to "ascertain if the unrefined and unpurified ethnobotanical substance (turmeric) retained the same active metabolites as the isolated active substance (curcumin)" (Ans. 7).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Ireson, Chattopadhyay, and Gilbert render the claims obvious?

Findings of fact

1. Ireson teaches that "[c]urcumin . . . is the major *yellow* pigment extracted from turmeric, the powdered rhizome of the herb *Curcuma longa*" (Ireson 1058, col. 1).

2. Ireson "tested the hypothesis that curcumin is biotransformed similarly by human and rat liver" (Ireson 1059, col. 1).

3. Ireson teaches

> hepatocytes [liver cells] obtained from humans and rats were incubated with curcumin, and their metabolites were identified. Curcumin was also administered to rats via the i.v. and p.o. routes, and its plasma metabolites were compared with those found in suspensions of liver cells. Finally, to investigate whether the identified metabolites possess pharmacological properties germane to chemoprevention, we compared their ability with that of curcumin to inhibit phorbol ester-induced COX-2 expression in human colon cells as reflected by PGE_2 levels.

(Ireson 1059, col. 1).

4. Ireson teaches step (1) of providing a ethnobotanical substance, specifically teaching the "following chemicals and reagents were purchased from the suppliers listed: curcumin" (Ireson 1059, col. 1).

5. Ireson teaches steps (2) and (3) of obtaining "hepatocytes from humans or rats" and these "[f]reshly isolated hepatocytes . . . were suspended in liver suspension medium (2 ml) and incubated in a slowly shaking incubator (37°C). Curcumin dissolved in DMSO was added to furnish a final concentration of 100 µM" (Ireson 1059, col. 2).

6. Ireson teaches steps (4) and (5) of comparison of the human and animal chemical entities and identifying matches as shown in Figure 2, reproduced below:

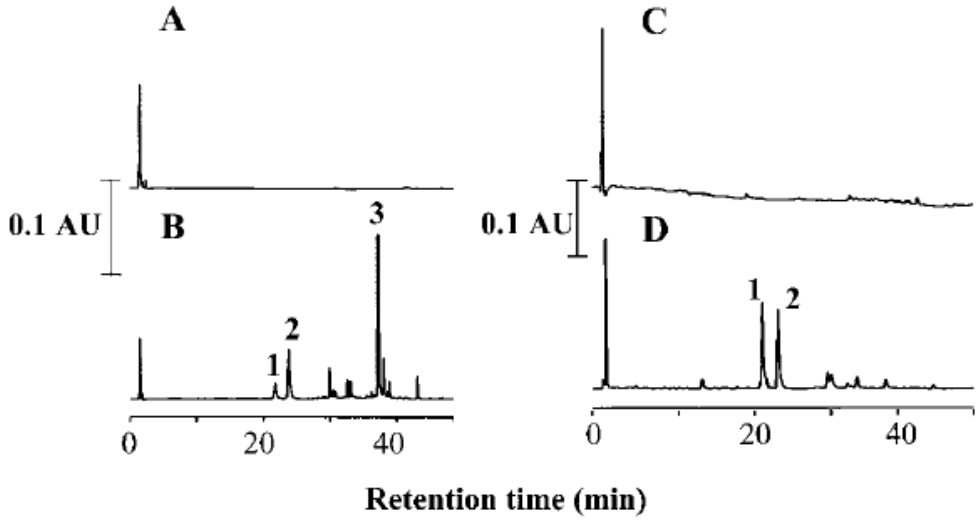

Fig. 2. High-performance liquid chromatograms with detection at 280 nm of extracts of suspensions of hepatocytes from humans (*A* and *B*) or rats (*C* and *D*) incubated for 2 h without (*A* and *C*) or with (*B* and *D*) curcumin (100 *µM*). Chromatograms are representative of incubations with six (rat) and four (human) separate hepatocyte preparations. Peaks were identified by cochromatography and mass spectrometry (see text) as curcumin (3), hexahydrocurcumin (2), and hexahydrocurcuminol (1).

(Ireson 1060, col. 2).

7. Ireson teaches step (6) of in vivo dosing where "[f]emale F344 rats received curcumin either p.o. (gavage, 500 mg/kg; vehicle, DMSO; dosage volume, 2.0 ml/kg) or i.v. (40 mg/kg; vehicle, glycerol formal; dosage volume, 1.0 ml/kg)" (Ireson 1059, col. 2).

8. Ireson teaches step (7) where "blood was removed by cardiac puncture 30 min and 1, 2, 6, 12, and 24 h (p.o. administration) or 5 and 30 min and 1 and 6 h (i.v. administration) after dosing" (Ireson 1059, col. 2).

9. Ireson teaches step (8) of analyzing the blood sample by separating plasma where "[e]xtraction efficiencies from plasma using the ethyl acetate extraction method for curcumin, hexahydrocurcumin, and curcumin sulfate were determined by HPLC" (Ireson 1059, col. 2).

10. Ireson teaches step (9) of comparing the chemical entities to analyze their medicinal activity, specifically teaching:

> (a) human and rat liver reduces curcumin first to hexahydrocurcumin and then to hexahydrocurcuminol, whereas conjugation of curcumin is only a minor hepatic biotransformation route; (b) the biotransformation step curcumin hexahydrocurcumin is rapid, and the overall rate of curcumin reduction seems slower in human than in rat liver cells; (c) the predominant metabolites of curcumin in rat plasma *in vivo* are curcumin glucuronide and curcumin sulfate, whereas hexahydrocurcumin and hexahydrocurcuminol, the major metabolites of curcumin in hepatocyte suspensions, occur only in small amounts in rat plasma after curcumin administration; (d) curcumin metabolites are markedly less able to inhibit inducible COX-2 expression than their metabolic progenitor.

(Ireson 1062, col. 2).

11. Chattopadhyay teaches "Turmeric (*Curcuma longa* L.) is a medicinal plant extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases" (Chattopadhyay 44, col. 1).

12. Chattopadhyay teaches "[i]n old Hindu medicine, it is extensively used for the treatment of sprains and swelling caused by injury" (Chattopadhyay 44, col. 1).

13. Chattopadhyay teaches "[t]urmeric powder, curcumin and its derivatives and many other extracts from the rhizomes were found to be bioactive" (Chattopadhyay 44, col. 2).

14. Chattopadhyay teaches "[s]everal pharmacological activities and medicinal applications of turmeric are known. Although curcumin has been isolated in the 19th century, extracts of the rhizomes of *C. longa* have been in use from the Vedic ages" (Chattopadhyay 45, col. 2).

15. Gilbert teaches

> elucidating the actual mechanism of action of drugs at the cell or even at the gene level have resulted in a rational explanation of the action of some medicinal plants. The traditionally used crude extracts can thus be compared for mode of action and effective dosage with their isolated or synthetic counterparts. Somewhat surprisingly it turns out that the isolated substance is often less active by itself than it is when retained in the mixture present in the plant.

(Gilbert 13, col. 2).

16. Gilbert provides a mechanism explaining why a natural compound may have lower activity after purification, teaching that "[p]lant tissues contain phospholipids but these may be lost partially or wholly in the extraction process. . . . if these lipophilicity promoting agents are conserved in the extract, then higher absorption rates and lower excretion rates can be expected" (Gilbert 15, col. 1).

17. Gilbert teaches an example showing "a considerable enhancement of the pharmacological activities of a standardised *Ginkgo biloba* extract when combined with phosphatidylcholine" (Gilbert 15, col. 2).

18. Gilbert teaches therefore that

> before discarding ancient traditional formulations incorporating several plants, it would be wise to check whether some of the components, apparently inactive in the particular use prescribed, may be contributing to bioavailability of active principles of other plant components of the formula. It has been noted above, for example, that curcumin appears as a Phase I inhibitor and also as an MDR inhibitor. It is not surprising therefore that *Curcuma* spp. which contain it are so often found in Ayurveda and other traditional medicines.

(Gilbert 18, col. 2 to 19, col. 1).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does not more than yield predictable results" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Ans. 3–8; FF 1–18) and agree that the claims are obvious over Ireson, Chattopadhyay, and Gilbert. We address Appellant's arguments below.

Appellant contends that: "Ireson does not begin with or involve roots, fruits, seeds, bark or leaves; rather it begins with a single, purified, refined compound (curcumin) which has already been identified as having medicinal qualities and is thus deemed worthy of further investigation"; that Chattopadhyay "is simply . . . historical knowledge and nothing more, concerning use of a particular plant, namely turmeric, for medicinal treatment"; and that "Gilbert is also simply historical information about the possible medicinal effects of certain plants" (App. Br. 6–7).

We find these arguments unpersuasive because "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

In this case, Ireson teaches a method to investigate medicinally active chemical entities in enthnobotanicals like curcumin (FF 3) using the steps of claim 1 (FF 4–10) while Gilbert teaches to compare crude plant extracts with isolated components in order to determine "whether some of the components, apparently inactive in the particular use prescribed, may be contributing to bioavailability of active principles of

other plant components of the formula" (FF 18). Thus, it is the combination of Ireson and Gilbert, along with Chattopadhyay's teaching that turmeric, the source of curcumin, is well known as a medicinal plant (FF 1214), that provides reason for the ordinary artisan to apply Ireson's method to plant sources including turmeric rhizomes (roots) (FF 1, 13, 18) in order to determine whether other turmeric components may improve the efficacy of isolated curcumin (FF 16–18).

Appellant contends that "the examiner fails to provide a reference or any reasoning that such a substitution would be obvious. In fact the lack of such a specific teaching, given the 'ancient history' pointed out by the examiner of the secondary references, is an indication that such a substitution in Ireson is in fact not obvious" (App. Br. 8).

We find this argument unpersuasive because, as discussed above, Gilbert provides a specific reason to investigate entire ethnobotanical sources for activity using methods such as the screening method of Ireson, because "traditionally used crude extracts can thus be compared for mode of action and effective dosage with their isolated or synthetic counterparts. Somewhat surprisingly it turns out that the isolated substance is often less active by itself than it is when retained in the mixture present in the plant" (FF 15). Ireson expressly teaches methods for comparing activity of different components to determine medicinal efficacy (FF 2, 3, 10) and the ordinary artisan, interested in analyzing whether crude extracts provide superior efficacy to isolated compounds would have reasonably selected Ireson's method, already shown effective on metabolites of the isolated ethnobotanical substance curcumin (FF 10).

Appellant contends that

> Gilbert simply teaches a plant per se as an alternative to an isolated compound thereof. There is no reason why one of ordinary skill would be motivated to make the substitution asserted by the examiner in the Ireson drug discovery process. The reasonable conclusion from Gilbert

> would be to consider using the plant (turmeric) per se as an alternative to purified curcumin only after purified curcumin was determined worthy of further investigation for possible human drug use, rather than in the Ireson process.

(Reply Br. 3).

We find this argument unpersuasive because claim 1 expressly states an interest in screening an "ethnobotanical substance comprising an existing land or marine plant source identified as having an active agent associated with a medicinal effect on humans." Thus, consistent with claim 1, the ordinary artisan, informed by Ireson that isolated curcumin, derived from turmeric rhizomes, functions as a medicinal compound that inhibits COX-2 (FF 1, 10), would have had reason based on Gilbert to test the original starting material for improved activity because Gilbert teaches that "it would be wise to check whether some of the components, apparently inactive in the particular use prescribed, may be contributing to bioavailability of active principles of other plant components of the formula" (FF 18).

That is, the arrangement of steps in the Examiner's reasoning (*see, e.g.*, Ans. 16–17) is substantially the same as the arrangement of steps recited by claim 1, where after a plant having an active medicinal effect is identified, the plant is subjected to screening to identify active chemical entities within the plant, just as Gilbert suggests in order to identify whether other components contribute to the activity of the already known chemical entity (FF 15, 18).

Appellant contends "[a]pplying the human-system based steps in the independent claims thus has the surprising benefit of identifying a broad array of active agents in ethnobotanical substances not otherwise discovered by the use of traditional chemical (non-human system based) fractionation methods" (App. Br. 8).

We find this argument unpersuasive because Appellant does not provide any evidence to support this argument. "[I]t is well settled that unexpected results must be

established by factual evidence. 'Mere argument or conclusory statements in the specification does not suffice.'" *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). We further note that Appellant fails to provide any comparison showing such a result with the closest prior art of Ireson, nor does Appellant provide a showing that any such advantage is commensurate in scope with a claim open to any ethnobotanical substance whatsoever. *See In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). Also, unexpected results must be "commensurate in scope with the degree of protection sought by the claimed subject matter." *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Ireson, Chattopadhyay, and Gilbert render the claims obvious.

B-C. 35 U.S.C. § 103(a)

Appellant does not separately argue the rejections including Lu and Barnes (*see* App. Br. 9–10). Having affirmed the obviousness rejection of claim 1 over Ireson, Chattopadhyay, and Gilbert for the reasons given above, we also find that the further combination with Lu or Barnes renders the dependent claims obvious for the reasons given by the Examiner (*see* Ans. 8–11).

CONCLUSION

In summary:

Claim(s) Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
1–7, 12, 13, 15, 17–23, 28, 29, 31, 33–39, 41	§ 103(a)	Ireson, Chattopadhyay, Gilbert	1–7, 12, 13, 15, 17–23, 28, 29, 31, 33–39, 41	
1–8, 12, 13–15, 17–24, 28–31, 33–41	§ 103(a)	Ireson, Chattopadhyay, Gilbert, Lu	1–8, 12, 13–15, 17–24, 28–31, 33–41	
1–7, 12, 13, 15–23, 28, 29, 31–39, 41, 42	§ 103(a)	Ireson, Chattopadhyay, Gilbert, Barnes	1–7, 12, 13, 15–23, 28, 29, 31–39, 41, 42	
Overall Outcome			1–8, 12–24, 28–42	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED