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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* PAOLO SENIN, IVO SETNIKAR, and  
LUIGI ANGELO ROVATI<sup>1</sup>

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Appeal 2015-001485  
Application 12/295,616  
Technology Center 1600

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Before ERIC B. GRIMES, TIMOTHY G. MAJORS, and DEVON  
ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a composition for oral administration having a beneficial effect on the cardiovascular system, which have been rejected as obvious and directed to non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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<sup>1</sup> Appellants identify the Real Party in Interest as ROTTAPHARM S.P.A.  
App. Br. 2.

## STATEMENT OF THE CASE

### *Background*

The Specification discloses:

The present invention relates to a formulation for oral administration, in the form of tablets or of powder for extemporaneous use, which is able to exert a beneficial effect on the cardiovascular system, owing to a combination of activities such as eulipidaemic, cholesterol-lowering and triglyceride-lowering, antioxidant and protective of the vasal endothelium and others connected with these directly or indirectly.

Spec. 1:1–5.

### *The Claims*

Claims 1–14 and 17–21 are on appeal. Claim 1 is illustrative and reads as follows:

1. A composition for oral administration having a beneficial effect on the cardiovascular system, comprising as active principles policosanol, red yeast and astaxanthin, characterized in that it further comprises berberine or an extract containing berberine.

App. Br. 19.

The following rejections are before us to review:

- A. Claims 1, 3–9, 11–14, and 17–21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Setnikar,<sup>2</sup> Gouni-Berthold,<sup>3</sup> and Jiang.<sup>4</sup> Ans. 2.
- B. Claims 1–12 and 17–21 are rejected under 35 U.S.C. § 101 as directed to patent ineligible subject matter. Ans. 12.

### OBVIOUSNESS

The Examiner finds that Setnikar discloses the “additive or potentiated effects and cardiovascular benefit of a composition comprising active principles policosanol, red yeast rice extract [] fermented with *Monascus purpureus* and astaxanthin,” along with “patho-physiology of cardiovascular disease,” “mode of action” and dosage of the principle components. Ans. 3. The Examiner also finds that Setnikar discloses “treatment regimen assays related to determining the efficacy of administered composition including **statistical analysis** of assay results” and a “**teaching, suggestion and motivation** for combining different active principles having different modes of action and their cardiovascular benefit in lowering serum cholesterol (TC) and low-density lipoprotein cholesterol (LDL).” *Id.* at 3. The Examiner cites Gouni-Berthold for the teaching of the therapeutic benefit of policosanol as a lipid-lowering agent and dosages for

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<sup>2</sup> Ivo Setnikar et al., *Antiatherosclerotic Efficacy of Policosanol, Red Yeast Rice Extract and Astaxanthin in the Rabbit*, 55 DRUG RES. (6) 312–17 (2005).

<sup>3</sup> Ionanna Gouni-Berthold et al., *Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent*, 142 AM. HEART J., (2) 356–365 (2002).

<sup>4</sup> Jiang et al., WO 2006/029577 A1, published Mar. 23, 2006.

such use as well as evidence that “policosanol potentiates the antithrombotic effects of other drugs such as fibrate and aspirin.” *Id.* at 4. The Examiner notes neither reference teaches the claimed composition further comprising berberine but cites Jiang for its disclosure of methods and compositions comprising berberine, red yeast rice extract, and other compounds useful in treating hyperlipidemia and providing cardiovascular benefits. *Id.* The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to modify the teachings of Setnikar and Gouni-Berthold to add berberine and other beneficial compounds as taught by Jiang. *Id.* at 5.

We agree with the Examiner that, based on the cited references, it would have been prima facie obvious to make a composition for the purpose of combining the beneficial cardiovascular effects of policosanol, red yeast, astaxanthin, and berberine or a berberine related or derivative compound. The primary references disclose use of policosanol, red yeast, and/or astaxanthin for the purpose of treating cardiovascular disease models and/or hyperlipidemia (Setnikar Abstract, p. 313, ¶¶ 2–3, col. 2; Gouni-Berthold Abstract, pp. 358–360). Setnikar teaches the additive or potentiated effects realized by combining these compounds. Setnikar p. 317, ¶ 3. Jiang discloses compositions containing a berberine compound for the prevention and treatment of hyperlipidemia, elevated cholesterol and/or cardiovascular disease in mammals. Jiang Abstract, ¶¶ 23, 123–125. Thus, it would have been obvious to add berberine to policosanol, red yeast, and astaxanthin to achieve cardiovascular benefits in addition to those demonstrated in Setnikar.

Appellants argue, however, that the Declaration of Ivo Setnikar (“Setnikar Dec.”) “has established that unexpectedly superior results are

obtained by the claimed formulation” and thereby rebut the Examiner’s prima facie case. App. Br. 7.

We agree with Appellants that the Specification provides evidence that the composition provided synergistic effects to recipients that were significantly greater than would have been expected from adding the known effects of the respective individual compounds, and the Examiner has not provided an adequate basis to show that the increased effect would have been expected.

Tables 1 and 2 of the Setnikar Dec. are reproduced below:

**TABLE 1 - % reduction blood parameters**  
*(with respect to Ath.feed)*

	<b>CT</b>	<b>LDL</b>	<b>TG</b>
<b>Berb 100</b>	87%*	89%*	66%*
<b>Berb 30</b>	15%	13%	43%*
<b>ASS</b>	79%*	84%*	27%
<b>COMB</b>	94%**	96%**	76%*

(\*): Significant with respect to Ath.feed (cf. TABLE 2)

(\*\*): Significant with respect to Berb.100 and Ass. (cf. TABLE 2)

Setnikar Dec. ¶ 14.

Table 1 shows the percentage reduction in blood levels of cholesterol (CT), low density lipoproteins (LDL) and triclycerides (TG) induced by the claimed composition (COMB), and of the same principal components taken individually (identified as ASS, Berb 30 and Berb 100) on rabbits that were rendered hypercholesterolemic and hypertriglyceridaemic prior to testing (ASS is “a composition for oral administration based on policosanol, red yeast (RY) and an antioxidant selected from astaxanthin and folic acid” Spec. 3:15–17). Setnikar Dec. ¶ 13.

**TABLE 2 – Absolute blood levels**

	CT (mmol/l)	LDL (mmol/l)	TG (mmol/l)
<b>Berb 100</b>	8.04*	6.25*	3.27*
<b>Berb 30</b>	52.57	49.42*	5.49*
<b>ASS</b>	12.99*	8.52*	7.03
<b>COMB</b>	3.71**(+)	2.27**(+)	2.31**(+)
<b>Ath.feed</b>	61.85	56.8	9.63
<b>Baseline</b>	1.5	0.71	0.70

(\*): Significant with respect to Ath.feed

(\*\*): Significant with respect to Berb.100 and Ass.

(+): Not significant with respect to baseline.

Setnikar Dec. ¶ 14.

Table 2 provides the absolute values of the blood parameters identified in Table 1, compared with those from the hypercholesterolemic and hypertriglyceridaemic rabbits and normal rabbits (baseline). Setnikar Dec. ¶ 14.

The results of use of the claimed composition are described as follows:

Looking by way of example at the values relating to cholesterol, the treatment with Comb (combination of the invention) reduces cholesterol to levels which [sic, which] do not differ significantly from the normal Baseline values of the cholesterol blood levels (3.71 mmol/l after treatment with Comb against 1.5 mmol/l of Baseline. Such an effect is not only sharply increased with respect[] to that obtained after individual treatment with both Berb 30 and Ass, which are components of the combination according to the invention, but cannot even be reached by using a berberine dose more than three times higher than that used in Comb (8.04 mmol/l with Berb 100 against 3.71 of Comb). The same considerations above also apply to the LDL and TG levels.

Setnikar Dec. ¶ 15.

In other words, these data show that rabbits treated with the compound mixture ASS or berberine improved the absolute blood levels for all parameters CT, LDL and TG, but that rabbits treated with the claimed composition COMB showed a statistically significant increase in the improvement of each parameter with respect to the components or the known ASS combination. The Specification states:

The potentiation of the reductions of the increases in CT and LDL following addition of 30 mg/kg/d of berberine to Ass was unexpected and very substantial. In fact, these reductions were greater than those induced by 100 mg/kg of berberine, whereas 30 mg/kg of berberine on its own was not able to reduce CT and LDL significantly. COMB also almost normalized TG and based on this parameter it was more effective even than Berb 100.

Spec 20:20–21:6.

The Examiner argues that the synergistic effect was in fact expected based on the additive effects shown in the prior art, and cites to references providing “methods for determination of ‘**synergy**’.” Ans. 8–10.

Although we agree that a skilled worker would reasonably expect the combination of policosanol, red yeast, astaxanthin, and berberine or an extract containing berberine to be more effective than either the combination represented by ASS or than any of these agents alone, we conclude that the Examiner has not provided a reasonable basis for concluding that the significant in vivo efficacy of the claimed composition (Setnikar Dec. ¶¶ 13, 14) would have been expected. We therefore conclude that Appellants have provided evidence of unexpected results that outweighs the evidence

supporting the prima facie case of obviousness. Accordingly, we reverse the rejection of claims 1, 3–9, 11–14, and 17–21 over Setnikar, Gouni-Berthold, and Jiang.

#### SUBJECT MATTER ELIGIBILITY

The Examiner finds that claims 1–12 and 17–21 “are directed to a naturally-occurring composition thereof, whether isolated or synthetic or not, that are not patent-eligible . . . as they are not markedly different than the compositions as it occurs [sic, they occur] in nature.” Ans. 12. The Examiner finds:

It is noted that the instant specification discloses that berberine is obtained from a natural vegetable source . . . and thus is a naturally occurring composition; policosanol is obtained from natural source such as beeswax, matrix of sugar cane, rice bran or various other plants . . . and thus is a naturally occurring composition; red yeast is the product of fermentation of rice by a fungus . . . and thus is a naturally occurring composition; astaxanthin is a reddish-orange pigment present in many living beings and especially in aquatic animals . . . and thus is a naturally occurring composition. . . . While claim 12 recites compositions in the form of tablets, capsules or powder for extemporaneous suspension of the naturally occurring substances, the only recited ingredient of the compositions of claim 12 is the active principles itself, i.e., policosanol, red yeast, astaxanthin, berberine and CoQ10 and thus these compositions are also not markedly different than the active principles as it occurs in nature and the mere aggregation of two naturally occurring products together does not change the structure of either product.

Ans. 12–13.

Appellants argue that “[t]he presently claimed composition provides a new utility by combining multiple compounds to provide a composition that

did not previously exist in nature while also providing a beneficial pharmaceutical composition. In other words, the presently claimed invention was not the mere discovery of nature’s handiwork.” Reply Br. 8.

We are persuaded that the claimed composition is patent eligible subject matter. Although the components are found in nature and can be isolated and combined, Appellants have shown by a preponderance of the evidence that the claimed composition differs significantly in effect from each of the compounds as it is known in nature. As discussed above, when formulated together, the claimed composition demonstrates an unexpected and significant synergistic effect. Setnikar Dec. ¶¶ 14, 15. Accordingly, we find the composition is patent eligible subject matter under the test set forth in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2017 (2013).

#### SUMMARY

We reverse the rejection of claims 1, 3–9, 11–14, and 17–21 as obvious over Setnikar, Gouni-Berthold, and Jiang and the rejection of claims 1–12 and 17–21 as directed to non-statutory subject matter.

REVERSED