UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/412,189	12/30/2014	Brian Cornblatt	2043-809	7985

1009 7590 06/29/2020

KING & SCHICKLI, PLLC
800 CORPORATE DRIVE, SUITE 200
LEXINGTON, KY 40503

EXAMINER	
NGUYEN, JOHN P	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
06/29/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

laura@iplaw1.net
uspto@iplaw1.net

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Ex parte BRIAN CORNBLATT, GRACE CORNBLATT, ANTON BZHELYANSKY, ROBERT HENDERSON, and RONALD KETTENACKER

_____

Appeal 2019-006022
Application 14/412,189
Technology Center 1600

_____

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and RACHEL H. TOWNSEND, *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 an oral composition composed of magnesium and broccoli extract or powder. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

---

[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 Nutramax Laboratories, Inc. (*see* Appeal Br. 3).

[2] We have considered and refer to the Specification of Dec. 30, 2014 ("Spec."); Final Action of Sept. 7, 2018 ("Final Act."); Appeal Brief of Feb. 19, 2019 ("Appeal Br."); Examiner's Answer of June 14, 2019 ("Ans."); and Reply Brief of Aug. 12, 2019 ("Reply Br.").

Statement of the Case

Background

"Oxidative stress plays a major role in aging, the progression of neurodegenerative diseases as well as physiological trauma, such as ischemia" (Spec. ¶ 7). "Antioxidant agents can reduce or inhibit the oxidation of vital biomolecules and may play a role in treating, preventing, or reducing the occurrence of conditions affected by oxidative stress" (*id.*). "An example of a natural product thought to have chemoprotective and antioxidant properties is sulforaphane. . . . The sulforaphane precursor, glucoraphanin, can be obtained from vegetables of the Brassicaceae family, such as broccoli, brussel sprouts, and cabbage" (*id.* ¶ 8). The Specification also teaches that "[m]agnesium is a mineral that is important for many systems in the body, including muscles and nerves" (*id.* ¶ 10).

The Claims

Claims 16–22, 26, and 27 are on appeal. Independent claim 16 is representative and read as follows:

> 16. An orally administrable composition comprising a synergistic combination of magnesium or a salt or complex thereof and a broccoli extract or powder comprising one or both of:
>
> a sulforaphane; and
>
> a sulforaphane precursor and an enzyme capable of converting the sulforaphane precursor to sulforaphane;
>
> the synergistic combination comprising the sulforaphane or sulforaphane precursor and the enzyme and the magnesium or a salt or complex thereof in amounts effective to decrease levels or decrease gene expression of monocyte chemoattractant protein-I (MCP-1) in a subject in need thereof.

The Issues

A. The Examiner rejected claims 16, 18–20, 22, 26, and 27 under 35 U.S.C. § 103(a) as obvious over Siddiqui,[3] Liang,[4] and Starrett[5] (Final Act. 4–7).

B. The Examiner rejected claims 17 and 21 under 35 U.S.C. § 103(a) as obvious over Siddiqui, Liang, Starrett, and Talalay[6] (Final Act. 7–9).

A. 35 U.S.C. § 103(a) over Siddiqui, Liang, and Starrett

The Examiner finds "Siddiqui discloses compositions comprising sulphoraphane and minerals such as magnesium and vitamin C" and "discloses the composition can be in tablet form" (Final Act. 5). The Examiner acknowledges that Siddiqui "fails to disclose sulforaphane or sulforaphane precursor and the magnesium or a salt or complex thereof in amounts effective to provide synergy in decreasing levels or decrease gene expression of MCP-1" (*id.*).

The Examiner finds "Liang discloses that sulforaphane reduces the incidence of a number of forms of tumor" and "Liang teaches that magnesium has a maximum inhibition on the formation of sulforaphane at 2 mM and that increasing the concentration of magnesium ion, the yield of

---

[3] Siddiqui et al., US 6,511,675 B2, issued Jan. 28, 2003.
[4] Liang et al., *Effects of metal ions on myrosinase activity and the formation of sulforaphane in broccoli seed*, 43 J. Molecular Catalysis B: Enzymatic 19–22 (2006).
[5] Starrett et al., *Sulforaphane inhibits de novo synthesis of IL-8 and MCP-1 in human epithelial cells generated by cigarette smoke extract*, 8 J. Immunotoxicology 150–8 (2011).
[6] Talalay et al., US 2009/0247477 A1, published Oct. 1, 2009.

sulforaphane increased slightly" (Final Act. 5). The Examiner finds "Starrett teaches that sulforaphane inhibits MCP-1 chemokine production (e.g. decrease gene expression of MCP-1) induced by cigarette smoking" (*id.*).

The Examiner finds the combination obvious "because magnesium is known to increase production of sulforaphane from glucoraphanin (e.g. sulforaphane precursor) in extracts of broccoli by myrosinase, and sulforaphane is known to inhibit MCP-1 chemokine production (e.g. decrease gene expression of MCP-1)" (Final Act. 6).

The issues with respect to this rejection are:

(i) Does a preponderance of the evidence of record support the Examiner's conclusion that the combination of Siddiqui, Liang, and Starrett render claim 16 obvious?

(ii) If so, has Appellant provided evidence of unexpected results that outweighs the evidence supporting the prima facie case of obviousness?

Findings of Fact

1. The Specification teaches the "sulforaphane precursor, glucoraphanin, can be obtained from vegetables of the Brassicaceae family, such as broccoli, brussel sprouts, and cabbage. . . . Glucoraphanin is converted into sulforaphane by a thioglucosidase enzyme called myrosinase, which occurs in a variety of exogenous sources such as *Brassicaceae* vegetables and endogenously in the gut microflora" (Spec. ¶ 8).

2. The Specification teaches "the use of a broccoli extract and/or powder, including but not limited to broccoli seed and sprout extracts and powders . . . more preferably about 750 μg to about 400 mg . . . of the broccoli extract" (Spec. ¶ 37).

3. The Specification teaches the "magnesium or a salt or complex thereof may be used. In some embodiments, the composition of the present invention comprises about 1 to about 1000 mg" of magnesium (Spec. ¶ 44).

4. Example 6 of the Specification tested cells to measure MCP-1 levels after treatment with LPS and with "(i) DMSO (vehicle control), (ii) 0.5 μM SFN, (iii) 2.5 mM $MgSO_4$, or (iv) the combination of 0.5 μM SFN and 2.5 mM $MgSO_4$" (Spec. ¶ 93). The Specification finds that "magnesium sulfate alone resulted in an approximately 16% decrease, sulforaphane alone resulted in an approximately 29% decrease, and the combination of magnesium sulfate and sulforaphane resulted in an approximately 53% decrease. This shows that the combination had a greater than additive effect in reducing MCP-1 levels" (*id.* ¶ 94).

5. Siddiqui teaches "a dietary supplement containing an effective amount of calcium, magnesium, folic acid, vitamins B6, B12, C, and E, and phytochemicals comprising sulphoraphane" (Siddiqui 4:34–37).

6. Siddiqui teaches the dietary supplement "may be formulated into tablets, powders, gels, or liquids" (Siddiqui 7:42–43).

7. Table 4 of Siddiqui is reproduced, in part, below:

	Formula 2	Formula 3
Magnesium, mg	450	310
Brassica Concentrate	100	25
AWP, mg	323	1035
Acerola Concentrate, mg	300	975
Citrus Bioflavanoids, mg	150	100
Grape Seed extract, mg	0	50
Spinach, mg	0	68.5
Broccoli Sprout Extract, mg	0	35

"Table 4 provides two additional embodiments of the invention, designated as Formulae 2 and 3. These embodiments are exemplary only, and the dosages may be altered without departing from the spirit and scope of the invention" (Siddiqui 6:49–52; 7:1–30).

8. Liang teaches: "Glucoraphanin . . . a glucosinolate found in broccoli . . . produces mostly sulforaphane . . . and nitrile when it is hydrolyzed by myrosinase" (Liang 19, col. 1).

9. Liang teaches "[i]ncreasing the concentration of magnesium ion, the yield of sulforaphane increased slightly" (Liang 21, col. 2).

10. Starrett teaches "[t]reatment with 5 μM SFN prior to the CSE exposure significantly reduced the production of IL-8 and MCP-1" (Starrett 153, col. 2).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id*. at 417.

Analysis

Prima facie obviousness

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 4–7; FF 1–10) and agree that claim 16 is rendered obvious by Siddiqui, Liang, and Starrett. We address Appellant's arguments below.

Appellant contends "no teaching of Siddiqui even hints of any synergistic effect of magnesium and sulforaphane or broccoli extract or

powder comprising sulforaphane or a precursor on chemokine production as required by the Appellant's independent claims" (Appeal Br. 10).

We find this argument unpersuasive for several reasons. First, Siddiqui teaches a composition of Formula 3 in Table 4 that is composed of 310 mg magnesium and 35 mg of broccoli sprout extract (FF 7). Siddiqui's composition contains an amount of magnesium falling within the 1 to 1000 mg magnesium range disclosed in the Specification (FF 3) and an amount of broccoli extract within the 750 µg to about 400 mg disclosed in the Specification (FF 2). Consequently, Siddiqui teaches an orally administrable composition comprising both claimed components in amounts disclosed by the Specification. (FF 2, 3, 7).[7] Thus, the prior art composition appears to be identical to that which is claimed to achieve a synergistic effect. "Using the same composition claimed . . . in the same manner claimed . . . naturally results in the same claimed . . . benefits." *Perricone v. Medicis Pharm. Corp*., 432 F.3d 1368, 1380 (Fed. Cir. 2005).

Second, as we address below in the unexpected results section, we are not persuaded that the evidence supports a finding of unexpected results.

Appellant contends Siddiqui "provides a broad and unfettered invitation to experiment but gives no other guidance to the skilled artisan in arriving at the Appellant's claimed subject matter" (Appeal. Br. 10). Appellant cites a case for the proposition that "a prior art reference offering 'a laundry list of potential active ingredients' could not by itself properly

[7] "It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002).

support a finding of obviousness" (*id.*; *citing Impax Labs. Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018)).

We are not persuaded. In *Impax*, the text immediately following that cited by Appellant explains the laundry list was composed of "'over twenty-five categories or examples of medications.'" *Impax*, 893 F.3d at 1379. *Impax* also finds that the drug at issue "is mentioned once, with no further mention in an example or claim." *Id.*

In the current case, Siddiqui not only recites sulphoraphane, broccoli extract, and magnesium multiple times but also provides a specific formulation that includes broccoli extract and magnesium together (FF 5, 7). Moreover, simply because the prior art "discloses a multitude of effective combinations does not render any particular formulation less obvious." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Here, Siddiqui exemplifies three particular formulas: Formula 1 includes sulphoraphane (*see* Siddiqui Table 1) and magnesium (*see* Siddiqui Table 3); Formula 2 has magnesium; and Formula 3 has both magnesium and broccoli extract (FF 7). Thus, two of the three exemplified formulas include the claimed ingredients. We do not find that Siddiqui represents a "laundry list" situation but rather provides substantial guidance to a more limited set of compositions that comprise sulphoraphane, broccoli extract, and magnesium (*see* FF 5).

Appellant contends that the Examiner "has grossly misinterpreted the teachings of Liang" and that "it cannot be fairly said that magnesium 'improves' conversion to sulforaphane because Liang expressly teaches that at <u>any</u> concentration tested magnesium had a net negative effect on conversion of glucoraphanin to sulforaphane when compared to 0 mM

magnesium" (Appeal Br. 11–12). Appellant notes, regarding Liang, that "synergy cannot rely on only slight or even additive effects of combinations of compounds. Instead, synergy as demonstrated by the Appellant requires more than simply an additive effect of a combination, i.e. a greater than expected result" (*id.* at 13).

We agree with Appellant's position that Liang does not provide a reason to combine magnesium and glucoraphanin. However, we need not rely upon Liang as supporting the obviousness analysis because Siddiqui teaches the combination of components required by claim 16 (FF 7). We note the Board may rely on less than all of the references applied by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961).

We are not, however, persuaded that Liang teaches away from the combination, because Liang does not address the impact of magnesium or sulforaphane or their combination on MCP-1 levels as required by claim 16. "Although a reference that teaches away is a significant factor to be considered in determining unobviousness, the nature of the teaching is highly relevant, and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Here, it may be that magnesium mildly reduces the conversion of glucoraphanin to sulforaphane, but this does not detract from Siddiqui's express teaching to use magnesium and broccoli extract together in a single, exemplary formulation (FF 7) that falls within the scope of claim 16.

Appellant contends:

> Due to the lack of any teaching or suggestion of synergy of magnesium and sulforaphane in the asserted art combination and the fact that the showing of synergy is only present on the record in the Appellant's specification, it logically follows that motivation to combine has been improperly gleaned from the Appellant's own specification and that the combination of Siddiqui, Liang, and Starrett is an exercise of impermissible hindsight.

(Appeal Br. 14–15).

We find this argument unpersuasive. First, as noted above, Siddiqui teaches a particular Formula 3 that comprises 310 mg magnesium (FF 7) falling within the 1 to 1000 mg magnesium range disclosed in the Specification (FF 3) and 35 mg broccoli extract (FF 7) falling within the 750 μg to about 400 mg disclosed in the Specification (FF 2). This express disclosure by Siddiqui is not hindsight, but existed prior to Appellant's filing date (FF 5, 7).

Second, while Appellant correctly notes that the synergy limitation is part of the claim, the "term 'synergistically effective amount' must mean any amount that is synergistic." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003). Appellant relies upon functional language and does not provide any specific details as to what amounts constitute a "synergistic" amount that functions to decrease levels or gene expression of MCP-1, though the Specification provides for ranges of the claimed compounds that are within the scope of the invention. Appellant provides a single in vitro example of a synergistic composition composed of 0.5 μM sulforaphane and 2.5 mM $MgSO_4$ (*see* FF 4). Notably, the Specification describes microgram to milligram amounts for broccoli

extract and milligram amounts for magnesium not molar amounts. Given the quantities of the claimed ingredients identified as being within the scope of the invention, the formula 3 composition of Siddiqui inherently satisfies the functional synergistic recitation in claim 16, absent evidence to the contrary. "Where, as here, the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Appellant has not provided any tests addressing the disclosure of Siddiqui.

Unexpected results

Appellant contends:

> A clear showing is made that the combination of sulforaphane and Mg had a synergistic effect on reduction in MCP-1 levels compared to either sulforaphane or Mg provided alone. Specifically, the combination of Mg and sulforaphane resulted in an approximately 53% decrease in MCP-1 levels compared to a 16% decrease in MCP-1 levels for Mg alone and a 29% decrease for sulforaphane alone.

(Appeal Br. 9).

We are not persuaded by the asserted unexpected result for several reasons. First, the data in the Specification is not compared with the closest prior art, which would be formula 3 of Siddiqui that contains both magnesium and broccoli extract (FF 7).[8] *See In re Baxter Travenol Labs*.,

[8] We note that because the amounts of magnesium and sulforaphane used in Example 6 of the Specification are reported as concentrations (0.5 μM SFN, 2.5 mM $MgSO_4$) without a disclosure of the volume added to cells, the Specification provides insufficient information to determine what mass amounts were used (i.e., milligrams or micrograms).

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.").

Second, 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). We are not persuaded that the results are commensurate in scope with claim 16 because the results are drawn to a single in vitro test employing 0.5 μM SFN and 2.5 mM $MgSO_4$, and no evidence that any other amount of these components would provide synergistic reduction in MCP-1 levels. We note that claim 16 is open to any amount of any type of magnesium salt, as well as any composition with any amount of either sulforaphane or any sulforaphane precursor and an enzyme that converts the sulforaphane precursor to sulforaphane, which when combined results in synergism "to decrease levels or decrease gene expression of" MCP-1." One data point is insufficient to "to ascertain a trend in the exemplified data which would allow [one having ordinary skill in the art] to reasonably extend the probative value thereof." *In re Kollman*, 595 F.2d 48, 56 (Fed. Cir. 1979).

Third, we are not persuaded that the data persuasively demonstrates the results of Example 6 are actually synergistic, and that the results represent a difference in kind rather than simply a difference in degree. We note that levels of MCP-1 "were assessed via quantitative RT-PCR" and the results are reported as a "percent of activated control." (Spec. ¶ 93.) When magnesium sulfate and sulforaphane are used together, the percent of activated control is stated to be 53% while magnesium sulfate alone is reported to be 16% and sulforaphane alone is reported to be 29% (FF 4).

When the two claimed component's values alone, 16% and 29%, are added, the additive effect is 45%. Appellant does not explain why the change of about 8%, from 53% to 45%, is a difference in kind rather than degree. We find these results do "not represent a 'difference in kind' that is required to show unexpected results." *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

Indeed, Appellant provides no evidence that the difference between 53% and 45% is statistically significant. Appellant has not provided any error bar in Figure 5 of the Specification, suggesting that the results represent a single experiment, and therefore Appellant has not demonstrated that the difference between 53% and 45% is reproducible and falls outside the ordinary variation expected during experimentation. *See McNeil-PPC, Inc. v. L. Perrigo Co*., 337 F.3d 1362, 1370 (Fed. Cir. 2003) (Finding evidence unpersuasive that "was based on the results of a study involving only nine participants and thus did not rise to the level of statistical significance" and finding the studies were "not shown to be reproducible.")

Conclusion of Law

(i) A preponderance of the evidence of record supports the Examiner's conclusion that the combination of Siddiqui, Liang, and Starrett render claim 16 obvious.

(ii) Appellant has not provided evidence of unexpected results that outweighs the evidence supporting the prima facie case of obviousness.

B. 35 U.S.C. § 103(a) over Siddiqui, Liang, Starrett, and Talalay

Appellant does not separately argue the rejection including Talalay (*see* Appeal Br. 15). Having affirmed the obviousness rejection of claim 16

over Siddiqui, Liang, and Starrett for the reasons given above, we also find that the further combination with Talalay renders the dependent claims obvious for the reasons given by the Examiner (*see* Final Act. 7–9).

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
16, 18–20, 22, 26, 27	103	Siddiqui, Liang, Starrett	16, 18–20, 22, 26, 27	
17, 21	103	Siddiqui, Liang, Starrett, Talalay	17, 21	
Overall Outcome			16–22, 26, 27	

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