

# Tryptophan-Ethylester, the False (Unveiled) Melatonin Isomer in Red Wine

Marcello Iriti<sup>1</sup> and Ileana Vigentini<sup>2</sup>

<sup>1</sup>Dipartimento di Scienze Agrarie e Ambientali, Università degli Studi di Milano, Milano, Italy. <sup>2</sup>Dipartimento di Scienze per gli Alimenti, la Nutrizione e l'Ambiente, Università degli Studi di Milano, Milano, Italy.

**ABSTRACT:** Among the food plants, the presence of melatonin in grapes (*Vitis vinifera* L.) deserves particular attention because of the production of wine, an alcoholic beverage of economic relevance and with putative healthy effects. Furthermore, melatonin isomers have been detected in wine too. Recently, one of these isomers has been identified as tryptophan-ethylester, a compound with the same molecular weight of melatonin. In this Commentary, we briefly comment the source(s) of tryptophan-ethylester in wine and the putative nutritional role(s).

**KEYWORDS:** tryptophan, melatonin, melatonin isomers, tryptophan-ethylester, red wine, grapes

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**CORRESPONDENCE:** marcello.iriti@unimi.it

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## Introduction

The topic of melatonin in grape products began less than a decade ago, when it was detected, for the first time, in berry skin of Italian and France grapevine varieties (*Vitis vinifera* L. cv. Barbera, Cabernet Franc, Cabernet Sauvignon, Croatina, Marzemino, Merlot, Nebbiolo, and Sangiovese) grown in north-western Italy.<sup>1</sup> Since then, indoleamine was reported in other grape tissues with varying levels according to both endogenous and exogenous factors, such as genetic traits, phenological stages, environmental and climatic conditions, and agricultural practices (Table 1). The presence of melatonin was also ascertained in red and white wine produced in different geographical areas (Table 1).

In the field of melatonin research, the occurrence of melatonin isomers in nature represents an emerging topic.<sup>2</sup> Isomers can be classified according to the position of the two side chains present in the indole ring of melatonin, the methoxy (M) group at position 5 and the N-acetylaminoethyl (A) group at position 3. Hypothetically, either one of these two side chains can be relocated to any one of the seven positions in the indole nucleus of melatonin to form isomers.<sup>3</sup> In particular, different isomers were found in grape products, including red wine, even if their chemical structure has not been identified yet.<sup>4–7</sup>

Very recently, in the attempt to determine the conformation of the most abundant (putative) melatonin isomer detected in red wine, we have identified it as tryptophan-ethylester, a compound with the same molecular weight of melatonin

(Fig. 1).<sup>8</sup> In particular, the concentrations of tryptophan-ethylester and melatonin in wine were 84 and 3 ng mL<sup>-1</sup>, respectively.<sup>8</sup> However, to date, the relationship between concentrations of melatonin and tryptophan-ethylester in grape products is still unknown: it seems that tryptophan-ethylester may arise from a pathway different from the melatonin biosynthetic route, possibly directly from tryptophan.

Amino acid esters readily cross cell membranes because of their lipophilicity and are subject to intracellular enzymatic hydrolysis, thus regenerating the native amino acids.<sup>9</sup> Therefore, dietary tryptophan-ethylester, a lipid-soluble tryptophan derivative, may bypass defective gastrointestinal neutral amino acid transport and be metabolized to melatonin in enteroendocrine cells of the gastrointestinal mucosa. In a child with Hartnup disease (an autosomic recessive metabolic disorder affecting the absorption of nonpolar amino acids, particularly tryptophan), tryptophan-ethylester administration successfully corrected tryptophan deficiency state, and *in vitro* experiments demonstrated that ester was hydrolyzed by intestinal mucosa, liver, and kidney to provide tryptophan.<sup>10</sup> More recently, in rats, tryptophan-ethylester, but not tryptophan, evoked a rapid and transient dose-dependent decrease in mean arterial pressure and heart rate and significantly promoted vasodilatation in small mesenteric arteries by blocking voltage-operated calcium channels on vascular smooth muscle cells.<sup>11</sup> Noteworthy, to the best of our knowledge, it seems that gut microflora has not the capacity to synthesize tryptophan-ethylester or melatonin isomers.

**Table 1.** Melatonin content in grapes and wine.

GRAPES	MELATONIN (NG G <sup>-1</sup> )	REFERENCES
Nebbiolo, Croatina, Barbera, Sangiovese, Marzemino, Cabernet Sauvignon, Merlot, Cabernet Franc (skin, Italy)	0.005–0.96	Iriti et al. <sup>1</sup>
Malbec, Cabernet Sauvignon, Chardonnay (skin, Argentina)	0.6–1.2	Stege et al. <sup>22</sup>
Merlot (whole berry, Canada)	100,000–150,000	Murch et al. <sup>23</sup>
Merlot (skin, Italy)	9.3–17.5	Vitalini et al. <sup>24</sup>
Merlot (seed, Italy)	3.5–10	Vitalini et al. <sup>24</sup>
Merlot (flesh, Italy)	0.2–3.9	Vitalini et al. <sup>24</sup>
Malbec (skin, Argentina)	9–159	Boccalandro et al. <sup>25</sup>
Malbec (skin, Argentina)	120–160	Gomez et al. <sup>5</sup>
Albana, Sangiovese (whole berry, Italy)	1.2, 1.5	Mercolini et al. <sup>26</sup>
Malbec (skin, Argentina)	440	Gomez et al. <sup>6</sup>
WINE	MELATONIN (NG ML <sup>-1</sup> )	REFERENCES
Albana, Sangiovese, Trebbiano (Italy)	0.6, 0.4	Mercolini et al. <sup>26,27</sup>
Chardonnay, Malbec, Cabernet Sauvignon (Argentina)	0.16–0.32	Stege et al. <sup>22</sup>
Groppello, Merlot (Italy)	8.1, 5.2	Vitalini et al. <sup>28</sup>
Cabernet Sauvignon, Merlot, Syrah, Tempranillo, Tintilla de Rota, Petit Verdot, Prieto Picudo and Palomino Fino (Spain)	5.1–420	Rodriguez-Naranjo et al. <sup>4,29</sup>

However, the exact contribution of grapes to melatonin, melatonin isomers, and tryptophan-ethylester in wine has not entirely been elucidated yet, and a pivotal role of yeasts and, possibly, of bacteria in the production of these metabolites in wine has been suggested. In a pioneering paper, Sprenger and colleagues demonstrated that, in *Saccharomyces cerevisiae*, melatonin is synthesized and metabolized to other 5-methoxylated indoles (5-methoxytryptamine and 5-methoxytryptophol).<sup>12</sup> In other yeast species, ie, *Saccharomyces uvarum* and *S. cerevisiae* var. *bayanus*, melatonin production in synthetic grapes must depend on growth conditions and medium, including tryptophan concentration.<sup>13</sup> Though no information is available on tryptophan-ethylester, the ability of yeasts to enrich indoleamine-fermented foods and beverages different from wine is corroborated by a number of studies.<sup>14–19</sup> In this view, these microorganisms may also contribute to the biosynthesis of tryptophan-ethylester in wine. Our preliminary results showed that high levels of tryptophan-ethylester are produced by yeasts in enological conditions.<sup>20</sup>

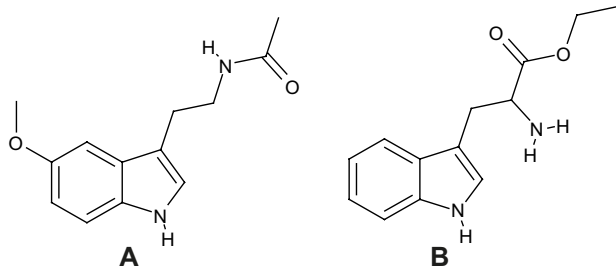
In conclusion, as the source(s) of tryptophan-ethylester in wine is(are) still unknown, we can only speculate on the putative nutritional role(s) of this compound: it may provide a pool of tryptophan able to cross the gastrointestinal tract and, possibly, the blood–brain barrier; then, de-esterified tryptophan-ethylester may be rapidly metabolized in target cells like enteroendocrine cells, which produce serotonin and melatonin, two paracrine and endocrine factors.<sup>21</sup> However, we have to take into account that pharmacologically active tryptophan-ethylester concentrations (5–20 mg/kg and higher) are unlikely to be reached in wines, at least based on current knowledge; therefore, we solicit further studies to quantify tryptophan-ethylester in a range of wines and grapes.

### Author Contributions

Conceived and designed the experiments: MI. Analyzed the data: MI, IV. Wrote the first draft of the manuscript: MI. Contributed to the writing of the manuscript: MI, IV. Agree with manuscript results and conclusions: MI, IV. Jointly developed the structure and arguments for the paper: MI, IV. Made critical revisions and approved final version: MI, IV. Both authors reviewed and approved of the final manuscript.

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**Figure 1.** Chemical structure of (A) melatonin and (B) tryptophan-ethylester.

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