# Effectiveness and safety of Monacolin K in patients with dyslipidaemia secondary to chronic renal disease

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**Summary** - This work is about the study on the effectiveness and safety of Monascus Purpureus (MP) in 1104 patients (387 women, 717 men, aged 70 on average) who suffer from dyslipidaemia secondary to chronic renal disease (CRD). The duration of the study was 2 years. Patients were divided by severity of renal disease into three groups (A, B, C). Group A was assigned 180 patients with an estimated glomerular filtration rate (eGFR) of 67 ± 16 ml/min/$m^2$. Group B consisted of 744 patients with moderate renal impairment and an eGFR of 38 ± 12 ml/min/$m^2$. Finally, group C, comprised 180 patients with severe renal impairment (eGFR = 19 ± 6 ml/min/$m^2$). The use of MP in this sensitive patient population has not only reduced LDL cholesterol and the risk of cardiovascular events, but has also contributed significantly to slowing down the progression of renal impairment.

**Key words: dyslipidaemia secondary to chronic renal disease, Glomerular kidney filtrate, albuminuria, cardiovascular risk.**

**Key messages:**

- Dyslipidaemia often complicates the cardiological risk in patients with chronic renal failure.
- Monascus Pupureus is a safe and effective alternative to statins for this group of patients.

## Introduction

Hypercholesterolemia is one of the main cardiovascular risk factors. At present, statins represent the best pharmacological solution to reduce plasma lipid levels. Unfortunately, for some patients, especially those suffering from chronic kidney disease, intolerance can occur in terms of myalgia either with or without increased CPK. Monacolin K is effective in reducing blood lipids (1). Since it also contain traces of a mycotoxin – citrinine, which is also known for its nephrotoxicity – the safety, tolerability and efficacy have been evaluated even in patients with dyslipidaemia secondary to chronic renal disease.

## Aim

The aim of this study is to evaluate the effectiveness and safety of specific MP dosage, notably 200 mg of dry extract in association with 10 mg of LAAS and 10 mg of Niacin, in patients with chronic renal failure at stages II, III, and IV according to the KDOQI classification (2)

## Materials and Methods

### *Patients*

1,104 outpatients with an average age of 70 ± 11.3 years were enrolled. Of those, 65% (717) were men, 35% (387) were women. The study lasted 2 years. Patients were divided into 3 groups (A, B, C) according to their renal function. Group A consisted of 180 patients with stage II chronic renal failure; Group B, the largest group of 744 patients with stage III CRF; and Group C, which consisted of 180 patients with stage IV chronic renal disease. (***Table 1***)

### *Exclusion Criteria*

Patients with haematological, hepatic, neoplastic, diabetic, and nephrotic proteinuria diseases were not considered.

### *Laboratory benchmarks*

The value of LDL cholesterol was obtained using the Friedewald formula. Non-HDL cholesterol was calculated using the following function: non-HDLC = TC - HDLC. The glomerular filtrate was measured according to the equation CKP-EPI (3)

### *Statistical analysis*

Parametric tests were used; all results were expressed as mean value ± standard deviation; mean values were compared using the Students' Test; statistical significance was assigned with values of p≤0.001.

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**Tab.1 - Patient characteristics: 1,104 patients with dyslipidaemia secondary to chronic renal disease.**

| Patients (# 1104) Groups | Male 65% (# 717) | Women 35% (# 387) | Age (70 ± 11), Age ± SD | CRI | GFR ml/min/m² |
|---|---|---|---|---|---|
| A (180) | 61.1% (110) | 38.8% (70) | 69 ± 10 | II° | 67 ± 16 |
| B (744) | 69% (514) | 31% (230) | 70 ± 13 | III° | 38 ± 12 |
| C (180) | 51.6% (93) | 48.3% (87) | 71.8 ± 11 | IV° | 19 ± 6 |

## Results

### *Group A*

Group A consisted of 180 patients, 110 men and 70 women, with an average age of 69 ± 10 years, with a renal function levels (eGFR) of 67 ± 16 mL/min/$m^2$ (***Table 1***). After 6 months of treatment, a significant reduction in TG (-21%), LDLC (-20%) and non-HDLC (-20%) was observed, respectively. At month 12, the following reductions were observed: TC (-22%), TG (-30%), LDLC (-28%), non-HDLC (-29%), and TC/HDLC (-28%). The same parameters further decreased at month 18: TC (-26%), TG (-35%), LDLC (-34%), non-HDLC (-34%), TC/HDLC (-33%). At the end of the study, after 24 months, the significant reductions were: TC (-31%) TG (-36.8%), LDLC (-42%), non-HDLC (-41%), and TC/HDLC (-40%). No changes in significant renal function (eGFR +2.5%) or HDLC (+13%) were observed (***Table 2***).

### *Group B*

Group B, the largest, consisted of 744 patients, 514 men and 230 women, with an average age of 70 ± 13 years, suffering from stage III chronic renal failure (eGFR 38 ± 12 mL/min/1.73 $m^2$) (***Table 1***). After 12 months of treatment, only triglycerides decreased significantly (-20%). After 18 months, significant reductions of non-HDLC (-23.2%), LDLC (-22%), TC/HDLC (-21.4%), TG (-28%) were observed. At the end of the study, lipid

**Tab. 2**

| Mounths | T0 | T6 | Δ% | P | T12 | Δ% | P | T18 | Δ% | P | T24 | Δ% | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **TC** | 25.4±41 | 212±23 | -15 | n.s | 196.2±39 | -22 | 0.001 | 186±62 | -26 | 0.001 | 172±83 | -31 | 0.001 |
| **HDLC** | 46±12 | 48±16 | 4.3 | n.s | 50 ± 21 | 8.6 | n.s | 51±18 | 10.8 | n.s | 52±35 | 13 | n.s |
| **TG** | 152±46 | 120±75 | -21 | 0.001 | 106±45 | -30 | 0.001 | 98±61 | -35 | 0.001 | 96±40 | -36.8 | 0.001 |
| **LDLC** | 175±38 | 140±47 | -20 | 0.001 | 125±52 | -28 | 0.001 | 115±62 | -34 | 0.001 | 101±51 | -42 | 0.001 |
| **non-HDLC** | 205±23 | 164±41 | -20 | 0.001 | 146±19 | -29 | 0.001 | 135±26 | -34 | 0.001 | 120±31 | -41 | 0.001 |
| **TC/HDLC** | 5.4 | 4.4 | -19 | n.s | 3.9 | -28 | 0.001 | 3.6 | -33 | 0.001 | 3.3 | -40 | 0.001 |
| **GFR** | 67±16 | 67.2±14 | 0.3 | n.s | 68±17 | 1.2 | n.s | 68.5±16 | 2.23 | 0.001 | 68.7±12 | 2.5 | 0.001 |
| **Albumin** | **neg** | **neg** | **n/a** | **n/a** | **neg** | **n/a** | **n/a** | **neg** | **n/a** | **n/a** | **neg** | **n/a** | **n/a** |

Group A: 180 patients with Stage II chronic renal failure (GFR = 67 ± 16 mL/min/$m^2$)
n.s. = statistically not significant
n/a = not applicable

parameters continued to decrease further as follows: TC (-27%), TG (-32%), LDLC (-33%), non-HDLC (-33.4%), TC/HDLC (-30%). Over the duration of the study, no patient showed a worsening of his/her renal function (eGFR +2.1%) (***Table 3***).

### *Group C*

Group C comprised 180 patients who suffered from severe renal failure (stage IV with eGFR of 19 ± 6 mL/min/1.73 $m^2$), of whom 93 were men and 87 were women with an average age of 71.8 ± 11 years. At the end of the 12-month period, significant reductions were observed in TC (-23%), TG (-31%), HDLC (-23%), non-HDLC (-26.8%), TC/HDLC (-25.2%). After 18 months: TC (-26%), TG (-36%), HLLC (-27%), non-HDLC (-31.8%), TC/HDLC (-32.4%). At the end of the study, the total reduction per parameter was: TC (-32%), TG (-38%), HDLC (-35%), non-HDLC (-38.5%), TC/HDLC (-40%). Also the patients of Group C showed no worsening of GFR renal function (+2.1%) (***Table 4***).

## Considerations

Alterations in the lipid profile are more prominent when the renal function is impaired. In turn, alterations of lipids and lipoproteins worsen the residual renal function by exposing nephropathic patients to greater risks of cardiovascular events (4, 5). Numerous studies confirmed that correcting dyslipidaemia is useful, as it improves proteinuria and holds back the decline of renal function in patients with chronic renal disease (6). In his meta-analysis, Douglas included the results on the effectiveness of hypolipidemic treatment in patients with severe albuminuria (7). Correcting dyslipidaemia, even with high doses of statins in patients with chronic renal disease can significantly slowed down the progression of renal damage, as widely demonstrated in the TNT (Treating to New Targets) study (8). It seems that the effectiveness of preventing the risk of cardiovascular events in patients with chronic renal disease treated with hypolipidemic therapy is higher than in patients with preserved renal function (9). In this study the efficacy and safety of nutraceutical MP in patients with different stages of chronic renal disease (mild, moderate and severe) was evaluated. From a safety point of view, no patient stopped treatment due to a worsening of his/her renal function (expressed as GFR ml/min) or to the onset of albuminuria during the 2 years of observation (***Tables 2, 3, 4***).

The results of this study show that – using the same dosage – the early hypolipidemic treatment in patients with chronic renal disease where lipid profile has been corrected slowed down the decline of renal function, especially during the first stages of chronic renal disease. Patients with stage II CRI show a LDLC decrease by -42% and a reduction in renal impairment by +1.7 mL/min/1.73$m^2$, compared to patients with stage III CRI who show a LDLC reduction by -33% and glomerular

**Tab. 3**

| MONTHS | T0 | T6 | Δ% | P | T12 | Δ% | P | T18 | Δ% | P | T24 | Δ% | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TC | 269.8±65 | 249.8±73 | -7.4 | n.s | 232 ± 59 | -14 | n.s | 218 ± 46 | -19 | n.s | 195.2±81 | -27 | 0.001 |
| HDLC | 42 ± 19 | 42.4 ± 22 | 0.95 | n.s | 43 ± 24 | 2.38 | n.s | 43.2± 31 | 2.9 | n.s | 43.5 ± 47 | 3.5 | n.s |
| TG | 184 ± 99 | 162± 152 | -12 | n.s | 147 ± 90 | -20 | 0.001 | 131±103 | -28 | 0.001 | 125 ± 94 | -32 | 0.001 |
| LDLC | 190 ± 48 | 174 ± 94 | -8.4 | n.s | 156 ± 56 | -18 | n.s | 148 ± 71 | -22 | 0.001 | 126 ± 34 | -33 | 0.001 |
| non-HDLC | 227.8±52 | 207.4±44 | -8.9 | n.s | 189 ± 39 | -17 | n.s | 174.8±63 | -23.2 | 0.001 | 151.7±33 | -33.4 | 0.001 |
| TC/HDLC | 6.42 | 5.89 | -8.2 | n.s | 5.39 | -16 | n.s | 5.04 | -21.4 | 0.001 | 4.48 | -30 | 0.001 |
| GFR | 38 ± 12 | 38.1 ± 16 | 0.26 | n.s | 38.5± 17 | 1.31 | 0.001 | 38.6± 16 | 1.57 | 0.001 | 38.8 ± 11 | 2.1 | 0.001 |
| Albumin | neg | neg | n/a | n/a | neg | n/a | n/a | neg | n/a | n/a | neg | n/a | n/a |

Group B: 744 patients with Stage III chronic renal failure (GFR 38 ± 12 mL/min/$m^2$)
n.s. = statistically not significant
n/a = not applicable

Tab. 4

| Mounths | T0 | T6 | Δ% | P | T12 | Δ% | P | T18 | Δ% | P | T24 | Δ% | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TC | 285 ± 57 | 251 ± 29 | -12 | n.s | 219 ± 32 | -23 | 0.001 | 210 ± 41 | -26 | 0.001 | 193.4±53 | -32 | 0.001 |
| HDLC | 35 ± 19 | 31 ± 16 | -11 | n.s | 36 ± 22 | 2.8 | n.s | 38.2± 29 | 9.1 | n.s | 39.8 ± 18 | 13 | n.s |
| TG | 222 ± 57 | 186 ± 63 | -16 | n.s | 152 ± 41 | -31 | 0.001 | 141 ± 59 | -36 | 0.001 | 137 ± 39 | -38 | 0.001 |
| LDLC | 196 ± 71 | 173 ± 96 | -11.7 | n.s | 151 ± 85 | -23 | 0.001 | 143 ± 94 | -27 | 0.001 | 126 ± 45 | -35 | 0.001 |
| non-HDLC | 250 ± 33 | 220 ± 42 | -12 | n.s | 183 ± 67 | -26.8 | 0.001 | 171.8±49 | -31.8 | 0.001 | 153 ± 56 | -38.5 | 0.001 |
| TC/HDLC | 8.14 | 8 | -0.56 | n.s | 6.08 | -25.2 | 0.001 | 5.49 | -32.4 | 0.001 | 4.85 | -40 | 0.001 |
| GFR | 19 ± 6 | 19.1 ± 5 | 0.52 | n.s | 19.25± 7 | 1.31 | 0.001 | 19.38± 2 | 2 | 0.001 | 19.42 ± 1 | 2.1 | 0.001 |
| Albumin | neg | neg | n/a | n/a | neg | n/a | n/a | neg | n/a | n/a | neg | n/a | n/a |

Group C:
180 patients with Stage IV chronic renal failure (GFR 19 ± 6 mL/min/$m^2$)
n.s. = statistically not significant
n/a = not applicable

filtrate of +0.8 mL/min/1.73$m^2$. Finally, patients with stage IV CRI showed a LDLC reduction by -35% with GFR = +0.42 mL/min/1.73$m^2$ (***Fig. 1***).

The effectiveness and safety of MP has been widely demonstrated in the literature, even in patients with heterozygous familial hypercholesterolemia (HeFH) with moderate cardiovascular risk who are intolerant to hypolipidemic drugs such as statins and ezetimibe (10). Mazza F. studied 55 patients, 21 men and 34 women, suffering from heterozygous familial hypercholesterolemia, with an average age of 53 years; 56% of patients had ultrasound-proven bilateral carotid thickening (<1.5 mm). All patients had previously experienced intolerance to treatment with statins (muscle pain, cramps with or without CPK increase). To ensure adequate control of LDL cholesterol values after suspending the administration of statins, the use of ezetimibe as an alternative drug has been proposed. The same patients stopped taking the drug again side effects similar to the previous treatment reappeared. For this reason, all patients are more vulnerable to increased risk of cardiovascular disease (Table 5). At the end of the 12-month study, all patients showed a statistically significant reduction in their lipid profile, and no patient abandoned the treatment with nutraceuticals because of intolerance (i.e., myalgia and increased liver or muscle enzymes) or to worsening renal function (Table 6). Halbert demonstrated that administrating 2.4 mg twice daily of MP in patients with hypercholesterolemia was as effective as administering 20 mg of pravastatin (11).

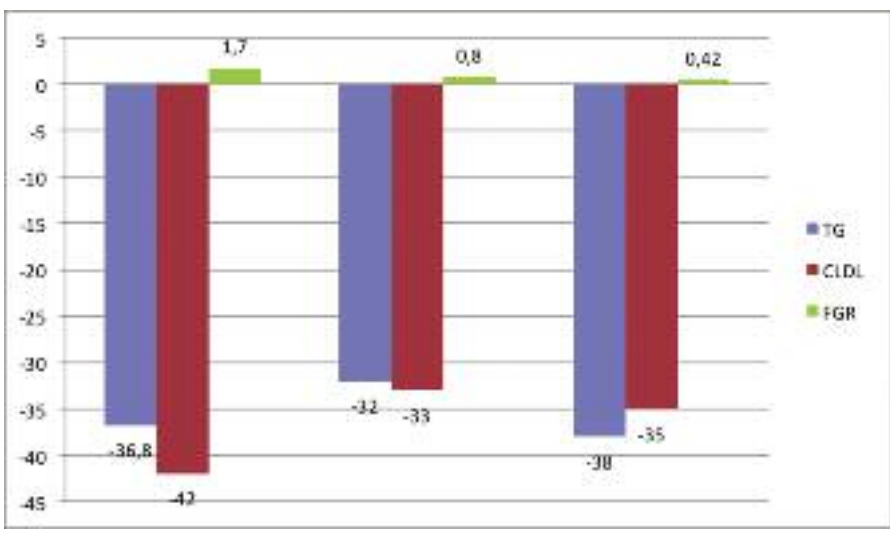


***Fig. 1*** - Reduction (in %) of triglyceride (TG) values, LDL cholesterol and (%) changes of glomerular filtrate (GFR) in patients with chronic renal disease: the earlier the hypolipidemic treatment begins, the best the therapeutic results will be at the same dosage.

**Tab. 5 - Characteristics of patients intolerant to statins and ezetimibe who stopped drug treatment due to the appearance of side effects**

| ParametERS | Gender | | P value |
|---|---|---|---|
| | Men | Women | |
| Number of patients | 21 | 34 | |
| Average age age ± SD | 52 ± 12 | 45 ± 18 | p<0.001 |
| BMI ± SD*, kg/m² | 24 ± 4 | 18 ± 3 | p<0.001 |
| Cramps e myalgia during treatment | Yes | Yes | |
| Carotid thickening | Yes | Yes | |

**Tab. 6 - Average reduction of lipids and lipoproteins in patients with familial hypercholesterolemia intolerant to statins and ezetimibe treated with MP for 12 months**

| Average lipids/lipoproteins values ± SD, mg/dL | Duration of the Study (12 months) | | | | | | |
|---|---|---|---|---|---|---|---|
| | T0 | T1 6 mo. | % | P value | T2 12 mo | % | P value |
| | Men | | | | | | |
| TC | 259 ± 18 | 223 ± 15 | -14 | <0.001 | 196 ± 11 | -24 | <0.001 |
| HDLC | 47 ± 5 | 48 ± 4.6 | 2 | ns | 48 ± 0.8 | 2 | ns |
| LDLC | 183 ± 18 | 151 ± 17 | -17 | <0.001 | 126 ± 11 | -31 | <0.001 |
| TG | 141 ± 14 | 115 ± 13 | -18 | <0.001 | 107 ± 6.3 | -24 | <0.001 |
| Non-HDLC | 211 ± 18 | 175 ± 16 | -17 | <0.001 | 147 ± 11 | -30 | <0.001 |
| | Women | | | | | | |
| TC | 248 ± 23 | 212 ± 13 | -14 | <0.001 | 179 ± 26 | -27 | <0.001 |
| HDLC | 65 ± 7 | 63 ± 8.5 | -3 | ns | 62 ± 2.7 | -4 | ns |
| LDLC | 154 ± 26 | 128 ± 15 | -16 | <0.001 | 95± 28 | -38 | <0.001 |
| TG | 140 ± 23 | 100 ± 11 | -28 | <0.001 | 104 ± 40 | -25 | <0.001 |
| Non-HDLC | 182 ± 25 | 148 ± 14 | -19 | <0.001 | 116 ± 26 | -36 | <0.001 |

## Conclusions

In this study, the effectiveness, tolerability, and safety of nutraceuticals in patients with dyslipidaemia secondary of chronic renal disease and moderate cardiovascular risk were proven. Nutraceuticals being studied represents a valid non-pharmacological alternative to control cholesterol.

Unfortunately, there are no safety studies on the use of PCSK9 inhibitors in patients with chronic renal failure. For this reason, in Italy, the use of nutraceuticals is a valid non-pharmacological therapeutic tool for a completely safe, constant, and effective control of LDL cholesterol values (12).

*Disclosures:*

The Author declares that he has no relationships relevant to the contents of this paper to Disclose.

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