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The Use of Ellagic Acid and *Annona muricata* Complex in Male Subjects with Oligospermia and HPV-Related Infections: Results from a Pilot Study

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Abstract: *Background*: Human papilloma virus (HPV) has been recognized as one of the most common sexually transmitted infections and has been correlated with poor semen quality and male hypofertility. Ellagic acid and *Annona muricate* have been considered as fascinating compounds in the chemoprevention of HPV-related lesions of the cervix. Here, we aimed to evaluate the role of ellagic acid and *Annona muricata* (OASIT-k®) in managing male subjects with oligospermia and HPV-related infections. *Methods*: From January 2017 to January 2019, all patients attending our center for oligospermia were evaluated for HPV-DNA. All HPV-DNA positive patients underwent orally administered OASIT-k 1 tablet/day for 3 months. After 6 months, all patients underwent spermiogram, HPV-DNA analysis on seminal plasma and urological visit. The main outcome measures were HPV-DNA clearance rate and improvement of semen parameters. *Results*: Forty-three patients (aged 22–43 years) were enrolled and treated. At the end of the treatment, the clearance of HPV-DNA infections was 62.7% (27/43). Seminal parameters were improved by treatment in terms of the number of spermatozoa (10.6 vs. 15.8) and mobility (27.5% vs. 36.1%). *Conclusions*: The therapy with OASIT-K was efficient in improving the HPV-DNA clearance and seminal parameters. These promising data emphasize the importance of redirecting the immune responses in viral infections.

Keywords: human papilloma virus; male fertility; HPV-DNA; ellagic acid; *Annona muricate*

Citation: Cai, T.; Tiscione, D.; Puglisi, M.; Gallelli, L.; Colosimo, M.; Rizzo, M.; Liguori, G.; Mazzoli, S.; Palmieri, A. The Use of Ellagic Acid and *Annona muricata* Complex in Male Subjects with Oligospermia and HPV-Related Infections: Results from a Pilot Study. *Uro* **2022**, *2*, 166–172. https://doi.org/10.3390/uro2030020

Academic Editor: Bartosz Malkiewicz

Received: 23 May 2022
Accepted: 1 July 2022
Published: 8 July 2022

1. Introduction

Human papilloma virus (HPV) has been recognized as one of the most common sexually transmitted virus infections, covering both oncogenic and non-oncogenic viruses [1]. The prevalence of any type of HPV in men has been estimated at about 49% and 35% of high-risk HPV [2]. The oncogenic role of HPV in males is well recognized, and the vaccination programs have led to a decrease in virus sharing, transmission and disease. HPV vaccine has been, then, demonstrated to be successful for preventing external genital lesions, genital warts in males and cervix cancer in women [3]. On the other hand, HPV infection in males has previously been associated with seminal decremental parameters by different authors [4–6]. The vaccines are able to prevent genital lesions and some kinds of

cancers both in men and in women, but there are no data about the effect of HPV vaccine on men affected by HPV infection and hypofertility [7,8]. Several experiences have been published about the role of some phytotherapic drugs in the management of HPV infections and related diseases. In particular, Morosetti et al. highlighted the clinical efficacy of *Annona muricata* and ellagic acid in the prevention of pre-neoplastic lesions of the cervix [9]. The clinical efficacy is probably due to the capability of *Annona muricata* and ellagic acid to induce cell-cycle arrest in the G1 phase, DNA reparation and apoptosis [10]. Moreover, *Annona muricata* seems to also have a protective role in Sertoli cells in the animal model and could be an interesting drug for male fertility [11]. Interesting findings have been reported for ellagic acid too [12]. In particular, Bucak et al. demonstrated that ellagic acid is able to reduce the oxidative stress parameters in ram semen, highlighting its probable protective role in spermatozoa [12]. The probable anti-oxidant effects of ellagic acid in combination with *Annona muricate* seem interesting in male fertility.

On the basis of this evidence, the aim of this study was to assess the role of ellagic acid and *Annona muricata* (OASIT-k®) in managing male subjects with oligospermia and HPV-related infections by using a pilot trial.

2. Materials and Methods

2.1. Study Design and Patient Population

The study design was in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials [13] and with the good clinical practice (GCP) guidelines. From January 2017 to January 2019, all patients attending our Urologic Department for confirmed diagnosis of oligospermia were evaluated for HPV-DNA and enrolled in this single-arm, self-controlled, interventional pilot study (Phase I study). All HPV-DNA-positive patients underwent orally administered OASIT-k® 1 tablet/day for 3 months and after one month after starting therapy were contacted by telephone to ensure the correct timing and treatment dose. At 3 months after completion of the medication, all patients underwent spermiogram, HPV-DNA analysis on seminal plasma and urological visit. The study schedule is summarized in Figure 1.

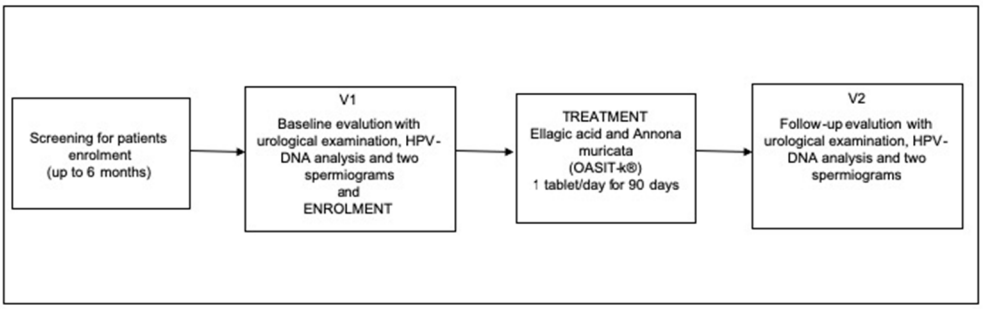

Figure 1. The study schedule.

2.2. Inclusion and Exclusion Criteria

The presence of HPV-DNA in the seminal plasma and a confirmed diagnosis of oligospermia in two consecutive spermiograms were considered the inclusion criteria. All male patients <18 and >45 years of age affected by major comorbidities and/or with evidence of other urological and/or andrological diseases were excluded. All patients testing positive for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, Herpes Viruses (HSV 1/2) and all patients who had undergone HPV vaccination were excluded too. All patients who were also candidates for medically assisted procreative procedures and all patients who underwent pharmacological drugs treatment to improve semen quality (i.e., estrogen blockers) were also excluded.

2.3. Outcome Measures

The following parameters were considered as the main outcome measures: HPV-DNA clearance rate, defined as the number of all patients with negative test for the individual HPV type following a positive test for that type, and the improvement of semen parameters, defined as a clinically significant improvement in any seminal plasma parameter.

2.4. Extract Composition and Characterization

Each administration of OASIT-k® contained 100 mg of ellagic acid and 100 mg of a dry extract from *Annona muricata*, as described in the manufacturer's instructions (Biostilogit, Florence, Italy).

2.5. Laboratory Considerations

All microbiological analyses were carried out according to the methods described by Mazzoli et al. [14] and Bartoletti et al. [15]. In brief, DNA extraction and purification were performed by DNeasy Tissue Kit by QIAGEN Spa, Milan, Italy. An amount of 200 µL of pellet was pre-incubated overnight by proteinase k and extracted and purified the day after in line with the manufacturer's instructions. The presence of genital HPV was evaluated by using Alpha Watch HPV, Alphagenic-Diaco-Biotechnology, Trieste, Italy. All the biological samples were analyzed by Inno-Lipa HPV Genotyping Extra (Innogenetics, Italy) [14,15]. In line with Mazzoli et al. and Munoz et al., we classified the following genotypes as high-risk HPV (HR-HPV): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82; as probable high-risk (PHR-HPV): 26, 53 and 66; and as low-risk (LR-HPV): 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 8118. HPV-positive samples, which did not hybridize with any of the type-specific probes, were referred to as positive non-genotype-able (PNG-HPV) [14,16]. All patients underwent two consecutive spermiograms. Semen collection and analysis were performed in the same laboratory, according to World Health Organization (WHO) 2021 Sixth Edition Manual [17]. In line with Cai T. et al. [4]., semen samples were collected directly in a sterile container by masturbation after 2–5 d of sexual abstinence. Semen parameters considered in this study were semen volume (millilitres), pH, sperm concentration (106/mL), percentage of motile sperm and percentage of normal morphologic forms.

2.6. Ethical and Statistical Considerations

This study was approved by the University of Catanzaro Institutional Review Board (number 48 of 22 February 2019). The study was conducted in line with good clinical practice guidelines and in compliance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all patients. The sample size calculation was not required due to the nature of the study; the pilot study (phase I) is defined as a small cohort of patients included in a first and preliminary analysis conducted before any large-scale quantitative research in order to evaluate the potential for a future, full-scale project [18]. However, the following statistical analyses were used: Student's *t*-test and the Mann–Whitney U-test for continuous variables, and χ^2 test for categorical variables, respectively. General characteristics of the study participants were reported using descriptive statistics. All *p*-values of < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS v22 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Characteristics

Forty-three patients (aged 22–43 years) were enrolled in this pilot study. All patients were positive in the HPV-DNA test. The mean spermatozoa count was 10.6 ($\times 10^6$/mL) (8.4–11.7); the median mobility percentage was 27.5 (24.3–29.6). No clinically significant alterations were reported at the sonography evaluation. All patients' baseline laboratory and clinical characteristics are displayed in Table 1.

Table 1. The demographic and clinical patient data at the baseline.

	Number or Median (Range or %)
Patients	43
Age	34 (22–43)
Educational qualification	
Primary School	1 (2.3)
High School	23 (53.4)
University	19 (44.3)
Sexual behavior	
1 partner	40 (93.1)
>1 partners	3 (6.9)
Sexual orientation	
Heterosexual	42 (97.7)
Homosexual	1 (2.3)
Testosterone (ng/dL)	
Total	635 (454–862)
Free	11.3 (7.48–14.76)
Total serum glucose level (mg/dL)	87 (77–99)
Sexually active (past month)	40 (93.1)
HPV genotypes	
HR-HPV	11 (25.5)
PHR-HPV	8 (18.7)
LR-HPV	7 (16.3)
PNG-HPV	17 (39.5)
Semen parameters	
Volume (mL)	2.9 (2.6–3.0)
pH	8.0 (7.8–8.1)
Sperm concentration ($\times 10^6$/mL)	10.6 (8.4–11.7)
Motility (%)	27.5 (24.3–29.6)
Morphology (normal forms) (%)	32.6 (28.1–37.4)

Normal value according to World Health Organization Laboratory Manual for the Examination of Human Semen and Sperm-cervical Mucus Interaction, 2021. HR-HPV = High-Risk HPV; PHR-HPV = Probable High-Risk HPV; LH-HPV = Low-Risk HPV; PNG-HPV = Positive Non-Genotype-able HPV.

3.2. Adherence to the Treatment

After one month, all patients (100%) were contacted by phone to ensure the correct timing and treatment dose, and all patients reported a high level of compliance with the treatment. No patients interrupted the treatment. No clinically significant adverse effects were reported.

3.3. HPV-DNA Clearence at 3 Months

At the end of the treatment, the clearance of HPV-DNA infections was 62.7% (27/43). The HPV-DNA clearance stratified for HPV genotypes is displayed in Table 2. The HPV genotypes classified as high-risk showed the lowest rate of HPV clearance.

3.4. Seminal Plasma Parameters

At the end of the follow-up period, seminal parameters were improved by treatment in terms of the number of spermatozoa (10.6 vs. 15.8) and mobility (27.5% vs. 36.1%). Subsequent analysis showed a strong correlation between the HPV-DNA clearance rate and the improvement of the number of spermatozoa (r = 0.78; $p < 0.001$).

Table 2. HPV-DNA analysis and semen parameters at 3-month follow-up visit.

	Baseline	**Follow-Up Visit**	***p***
HPV-DNA positive patients	43 (100)	16/43 (37.2)	
HPV genotypes			<0.001
HR-HPV	11 (25.5)	9/16 (56.2)	

Table 2. *Cont.*

	Baseline	Follow-Up Visit	*p*
PHR-HPV	8 (18.7)	2/16 (12.5)	
LR-HPV	7 (16.3)	2/16 (12.5)	
PNG-HPV	17 (39.5)	3/16 (18.8)	
Semen parameters			
Volume (mL)	2.9 (2.6–3.0)	3.0 (2.9–3.3)	0.79
pH	8.0 (7.8–8.1)	8.1 (7.9–8.3)	0.80
Sperm concentration ($\times 10^6$/mL)	10.6 (8.4–11.7)	15.8 (14.9–17.1)	<0.001
Motility (%)	27.5 (24.3–29.6)	36.1 (34.9–37.8)	<0.001
Morphology (normal forms) (%)	32.6 (28.1–37.4)	33.9 (33.1–34.0)	0.64

Normal value according to World Health Organization Laboratory Manual for the Examination of Human Semen and Sperm-cervical Mucus Interaction, 2021. HR-HPV = High-Risk HPV; PHR-HPV = Probable High-Risk HPV; LH-HPV = Low-Risk HPV; PNG-HPV = Positive Non-Genotype-able HPV.

4. Discussion

4.1. Main Findings

In this pilot study, for the first time, it was demonstrated that an association between *Annona muricata* and ellagic acid (OASIT-k®) is able to improve the HPV-DNA clearance and seminal parameters in terms of the number of spermatozoa and mobility.

4.2. Results in the Context of Previous Studies

Several authors demonstrated that ellagic acid and *Annona Muricata* are able to control the cell cycle and promote apoptosis [18,19]. Moreover, several studies showed that phytotherapy compounds are able to exert a protective influence against HPV persistence, with an interesting role in the chemoprevention of cervix cancer [19,20]. In particular, Morosetti et al. demonstrated a protective role of ellagic acid on cervical cells through apoptosis, cell-cycle arrest and repair mechanisms [9]. Here, the attention was focused on the protective and anti-oxidant role of ellagic acid and *Annona Muricata* in HPV-DNA clearance and seminal parameters improvement. No specific data about the role of ellagic acid and *Annona Muricata* complex in HPV-DNA clearance have been reported until now. However, we could elaborate some hypotheses for supporting our results. Firstly, the cell protective role of ellagic acid and *Annona Muricata* complex through cell-cycle arrest and repair mechanisms could reduce HPV replication and diffusions to the host cells and allow the immune system to improve HPV-DNA clearance. HPV-DNA clearance is an important key point of HPV infection in males [15] because it relates to HPV replication and the effect on human cells. In this sense, an earlier HPV-DNA clearance may be associated with less spermatozoa damage by HPV infection. On the other hand, the anti-oxidant effects of ellagic acid and *Annona Muricata* complex may protect the host cells from biological insults deriving from endogenous and exogenous free radicals. In this sense, the ellagic acid and *Annona Muricata* complex seem to be effective in improving seminal parameters, probably through anti-oxidant effects. Several authors reported that numerous reactive oxygen classes have been involved in seminal plasma parameters decline [21,22]. In particular, some metabolites in peroxidative damage are associated with oligospermia and teratospermia [23], such as prostate tissue damage [24,25]. In this sense, the use of anti-oxidant drugs is an important pillar in the management of hypofertile males. Ellagic acid and the *Annona Muricata* complex seem, then, to be effective in improving HPV-DNA clearance and improving seminal parameters through the cell-cycle regulation, repair mechanisms and anti-oxidant effects.

4.3. Strengths and Limitations

This study was planned as a pilot study (Phase I), and in this sense, some limitations are included in the nature of the study, such as the lack of a control group and the lack of sample size calculation. The small cohort of patients included in this analysis should be considered a limitation. On the other hand, in this study, we found some strengths,

such as the standardized methodology for analyzing HPV-DNA in seminal plasma and the appropriate follow-up time for evaluating the effect on seminal parameters. Further, larger studies are required to validate these preliminary findings.

5. Conclusions

In conclusion, the therapy with OASIT-K is efficient in improving HPV-DNA clearance and seminal parameters. These promising data emphasize the importance of redirecting the immune responses in viral infections.

Author Contributions: Conceptualization, T.C.; methodology, D.T., M.P. and L.G.; formal analysis, T.C., M.C.; investigation, M.R.; writing—original draft preparation, T.C.; writing—review and editing, G.L., A.P.; supervision, S.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was approved by the University of Catanzaro Institutional Review Board (number 48 of 22 February 2019). The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent Statement: Written informed consent was obtained from the patients to publish this paper.

Conflicts of Interest: The authors declare no conflict of interest.

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